Multi-Ensemble Markov Models and TRAM

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Outline

- Free energies
- Simulation types
  - Boltzmann reweighting
  - Umbrella sampling
  - multi-temperature simulation
  - accelerated MD

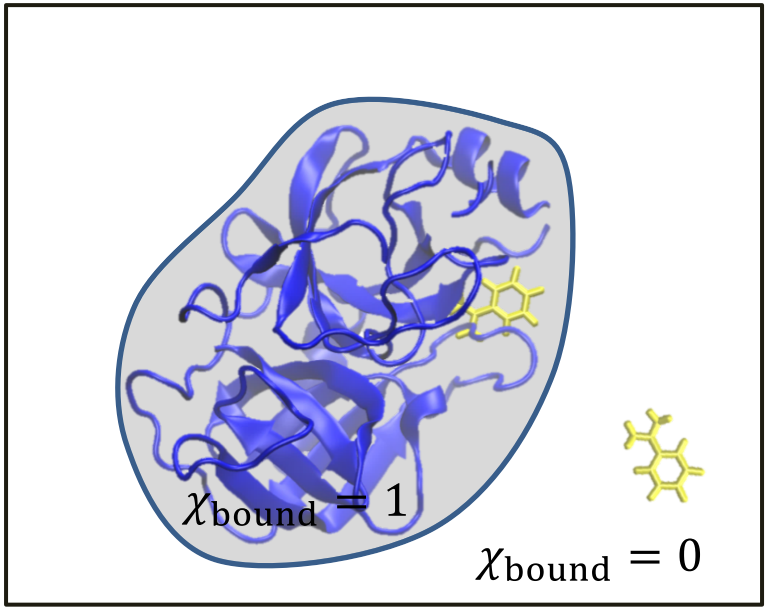
- Analysis methods
  - Weighted Histogram Analysis method + its problems
  - Multi Ensemble Markov Models and discrete TRAM

Free energy: definition and use

By “free energies” we mean :

A) – $k_B T$ times the logarithm of probabilities of different conformational states within one thermodynamic ensemble

$$P(\text{bound}) = \frac{\int \chi_{\text{bound}}(x) e^{-\beta U(x)} \mathrm{d}x}{\int e^{-\beta U(x)} \mathrm{d}x}$$

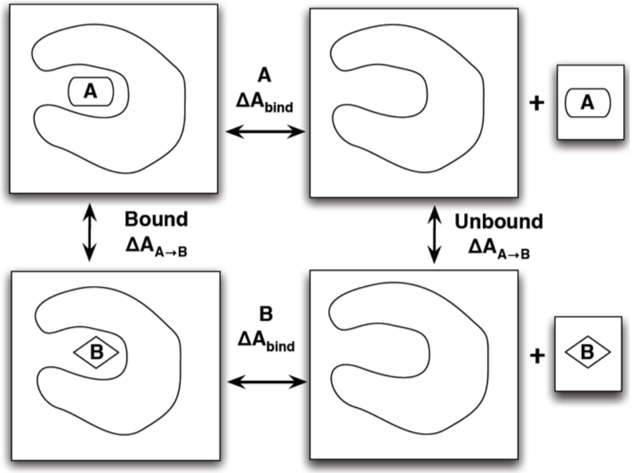


B) – $k_B T$ times the log of ratios of partition functions from different thermodynamic ensembles

$$e^{-\beta^{(1)} F^{(1)} + \beta^{(2)} F^{(2)}} = \frac{Z^{(1)}}{Z^{(2)}} = \frac{\int e^{-\beta^{(1)} U^{(1)}(x)} \mathrm{d}x}{\int e^{-\beta^{(2)} U^{(2)}(x)} \mathrm{d}x}$$

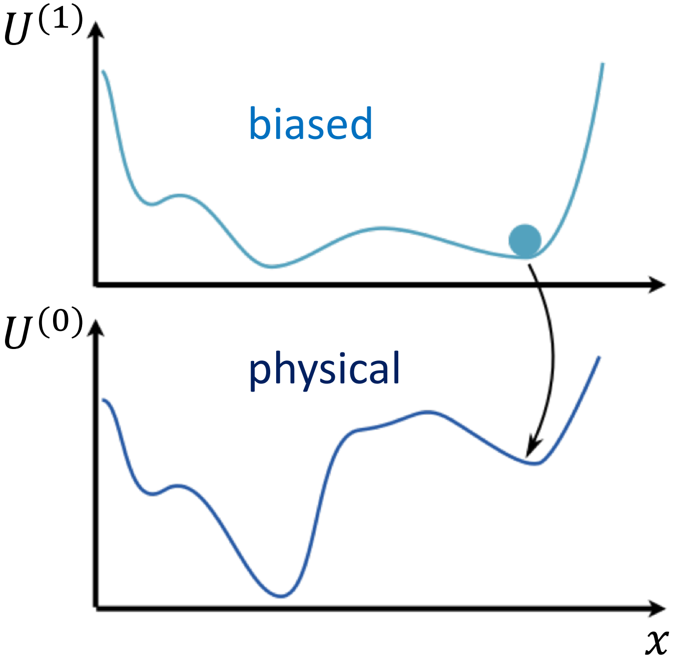
Uses:

- calculating entropy $S = -\left(\frac{\partial F}{\partial T}\right)_{V,N}$ or
- relative binding / solvation free energy



Boltzmann reweighting / importance sampling

Some systems have an interesting but improbable state or states that are separated by a high barrier. How can we investigate such states?



Expectation values in ensemble (0) are computed as:

$$\langle O\rangle^{(0)} = \int O(x)e^{-\beta U^{(0)}(x)+\beta F^{(0)}}\mathrm{d}x \approx \frac{1}{N}\sum_{n}^{N} O(x_n)$$

where $\boldsymbol{x}_n \sim p^{(0)}(\boldsymbol{x})$

$$\langle O\rangle^{(0)} = \int O(x)e^{-\beta U^{(1)}(x)+\beta F^{(1)}} \frac{e^{-\beta U^{(0)}(x)+\beta F^{(0)}}}{e^{-\beta U^{(1)}(x)+\beta F^{(1)}}}\mathrm{d}x$$

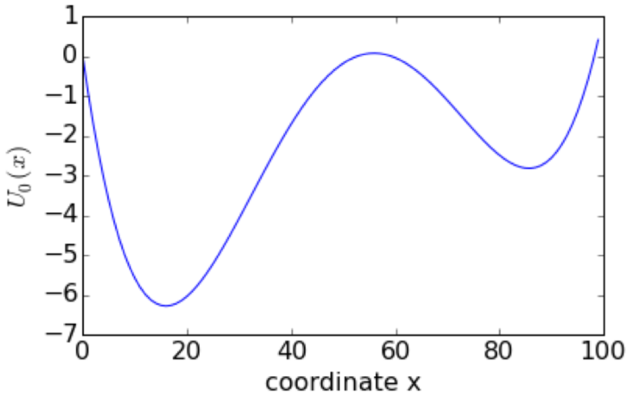
$$\approx \frac{1}{N}\sum_{n}^{N} O(x_n)e^{-\beta U^{(0)}(x)+\beta U^{(1)}(x)+\beta F^{(0)}-\beta F^{(1)}}$$

where $\boldsymbol{x}_n \sim p^{(1)}(\boldsymbol{x})$

- $U^{(0)}(x)$= the *unbiased* or the *physical* energy
- $U^{(1)}(x)$= the *biased* energy
- $U_{\text{bias}}^{(1)}(x) = U^{(1)}(x) - U^{(0)}(x)$= the *bias* energy

Boltzmann reweighting / importance sampling

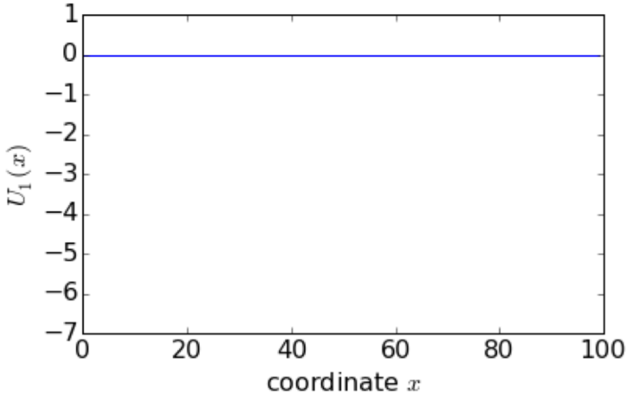
- $U^{(0)}(x)$= the *unbiased* or the *physical* energy
- $U^{(1)}(x)$= the *biased* energy
- $U^{(1)}_{\text{bias}}(x) = U^{(1)}(x) - U^{(0)}(x)$= the *bias* energy



What is the optimal bias?

For a low-dimensional system, it would be efficient to sample from a flat energy landscape:

$$U^{(1)}(x) = 0$$

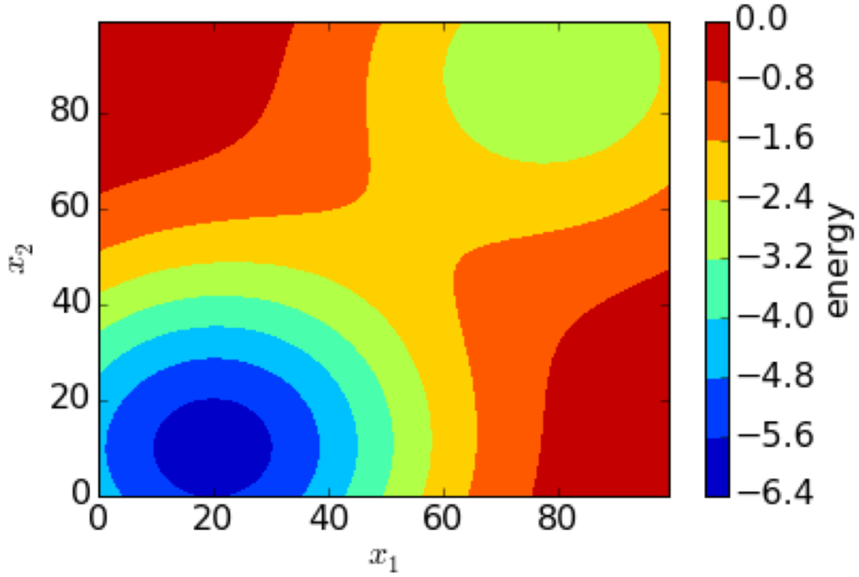


Allows good sampling of the minima and the barrier.

$$\Rightarrow U^{(1)}_{\text{bias}}(x) = -U^{(0)}(x)$$

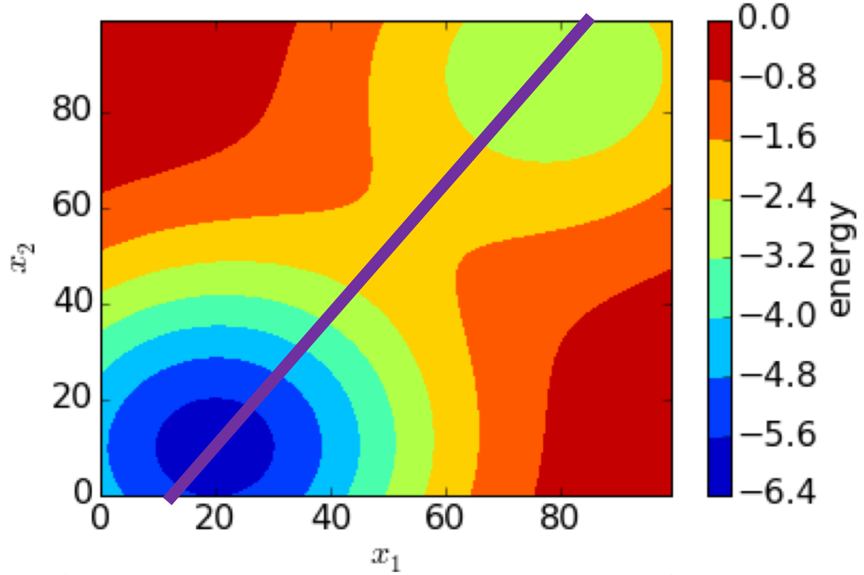
Importance sampling in high dimensions

- Sampling uniformly is not possible in high dimensional space like the conformational space.



Importance sampling in high dimensions

- Introduce an "order parameter" that connects the relevant minima in the energy landscape.

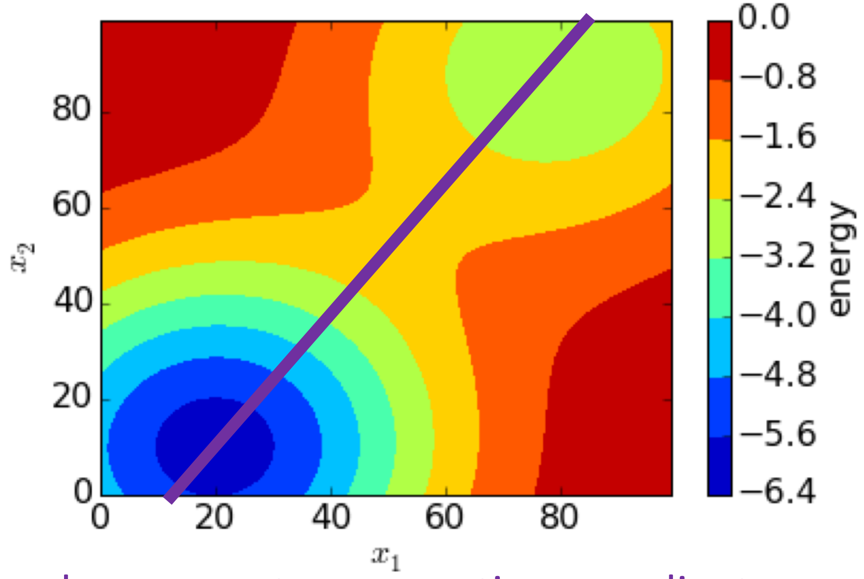


order parameter or reaction coordinate

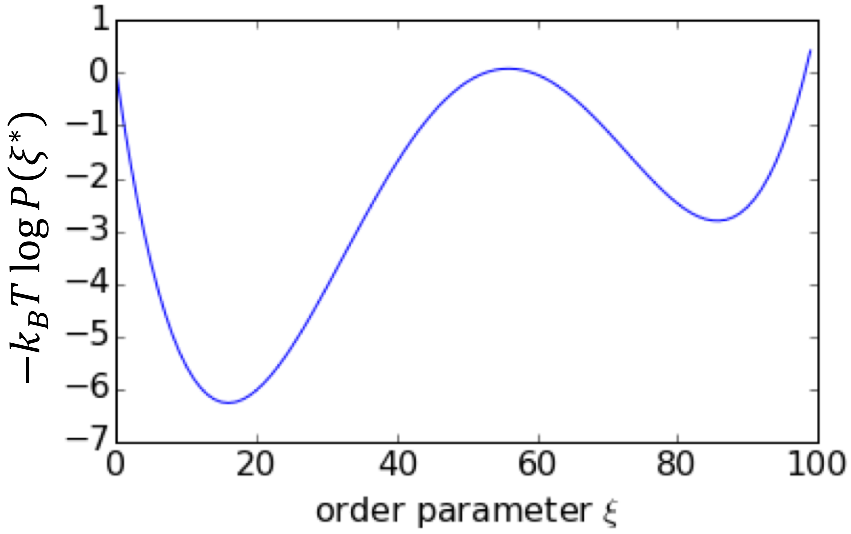
Importance sampling in high dimensions

- Sample uniformly along the order parameter.

$$P(\xi^*) \propto \int \delta(\xi(x) - \xi^*) e^{-\beta U(x)} \mathrm{d}x$$



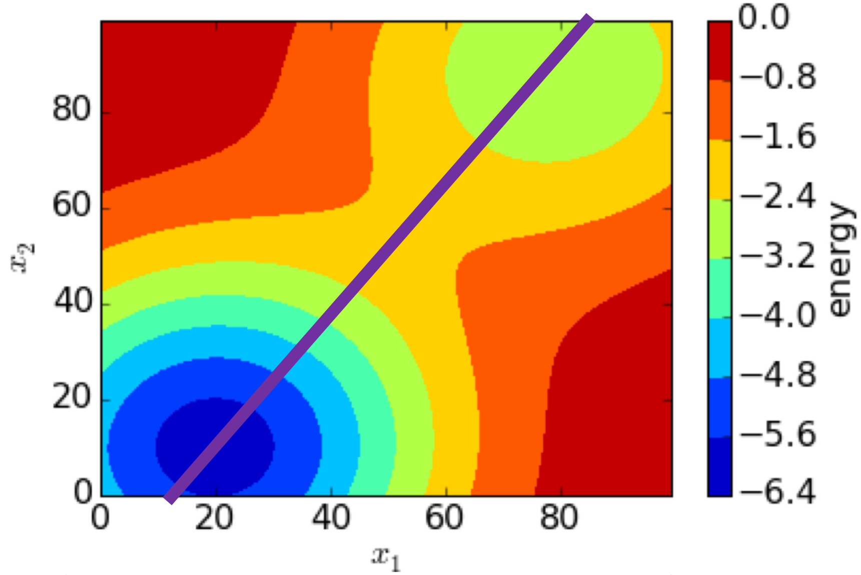
order parameter or reaction coordinate



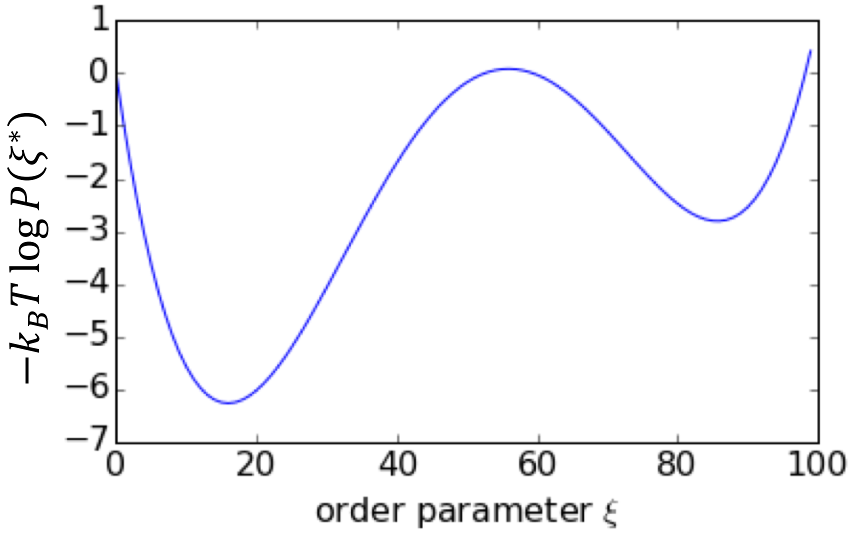
Importance sampling in high dimensions

- The ideal bias energy would be $k_B T \log P(\xi)$ (minus the potential of mean force)
- Problem: computing $P(\xi)$ requires sampling from the unbiased distribution!

$$P(\xi^*) \propto \int \delta(\xi(x) - \xi^*) e^{-\beta U(x)} \mathrm{d}x$$

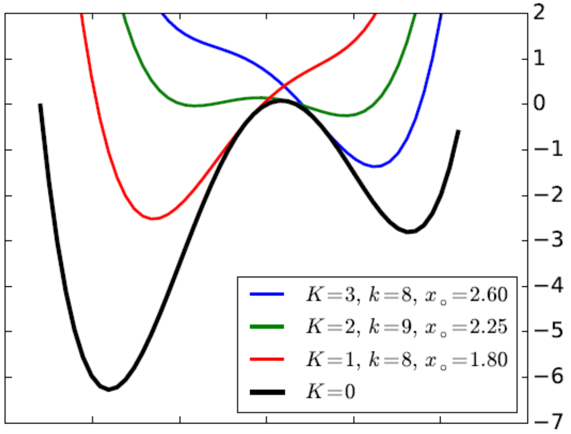


order parameter or reaction coordinate



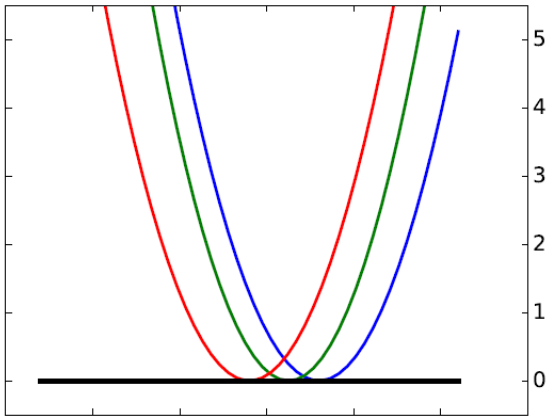
Umbrella sampling

- The ideal bias energy would be $k_B T \log P(\xi)$
- Problem: computing $P(\xi)$ requires sampling from the unbiased distribution!
- Instead of simulating with the ideal bias $k_B T \log P(\xi)$, we select a sub-optimal but *flexible* form of the bias. → umbrella sampling
- Use K different bias potentials that *jointly* allow uniform sampling.



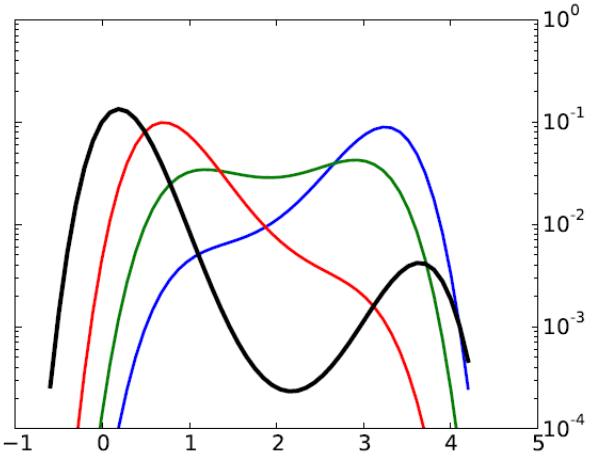
biased potentials

$U_0(x) + U_{\text{bias}}^{(k)}(x)$



bias potentials

$U_{\text{bias}}^{(k)}(x)$

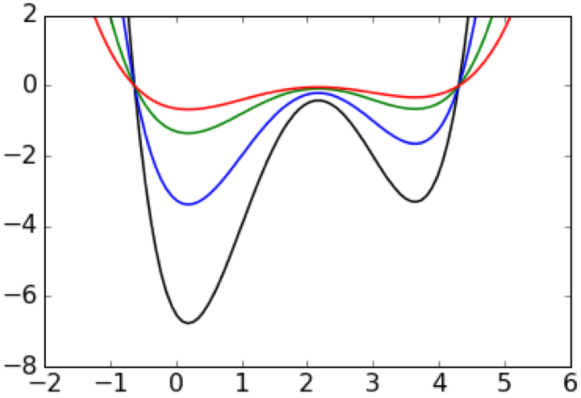


probability distributions

$P_{\text{biased}}(x) \propto e^{-\beta[U^{(0)}(x)+U_{\text{bias}}^{(k)}(x)]}$

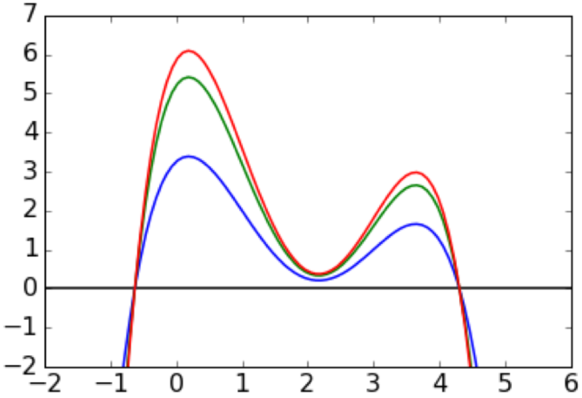
Multi temperature simulation

- Multi-temperature simulations is another way of approximately producing a flat biased distribution.



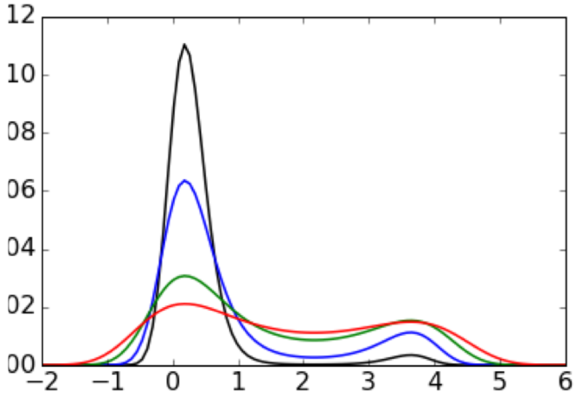
biased potentials

$\frac{\beta^{(k)}}{\beta^{(0)}} U^{(0)}(x)$



“bias potentials”

$\frac{\beta^{(k)}-\beta^{(0)}}{\beta^{(0)}} U^{(0)}(x)$



probability distributions

$P_{\text{biased}}(x) \propto e^{-\beta^{(k)} U^{(0)}(x)}$

- Idea has to taken with a grain of salt: order parameter and the minima that it connects are assumed to stay the same for all temperatures.

A bit of notation…

- Introduce “dimension-less bias“

$$b^{(k)}(x) \equiv \beta^{(k)}U^{(k)}(x) - \beta^{(0)}U^{(0)}(x)$$

  by picking the ensemble 0 as the reference ensemble.
- Assume that the energies in the reference ensemble are shifted, such that its Boltzmann distribution is normalized $\beta^{(0)}F^{(0)} = 0$.
- Introduce the log partition function $f^{(k)} = \beta^{(k)}F^{(k)}$

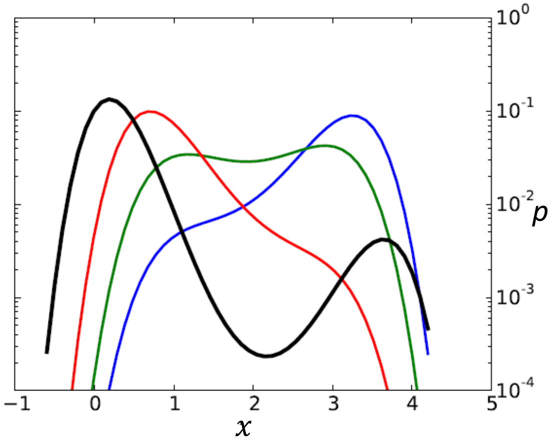
Then the reweighting factors become

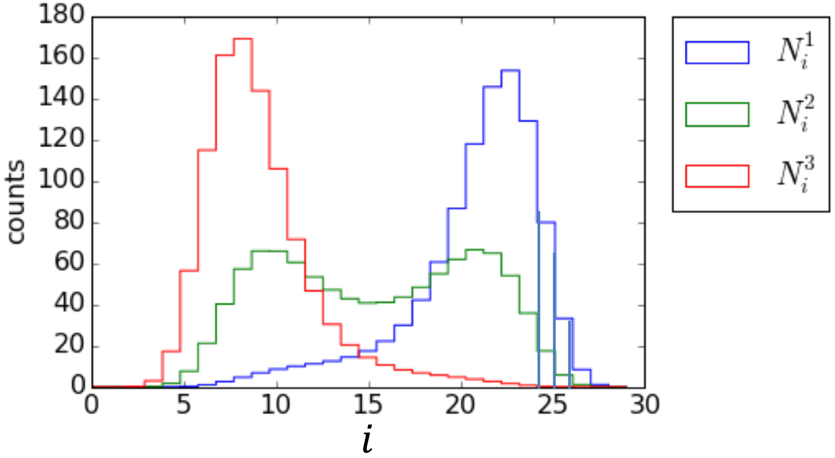
$$e^{-\beta^{(k)}U^{(k)}(x)+\beta^{(0)}U^{(0)}(x)+\beta^{(k)}F^{(k)}-\beta^{(0)}F^{(0)}} = e^{-b^{(k)}+f^{(k)}}$$

WHAM

Weighted **H**istogram **A**nalysis **M**ethod

The MD simulation gives us *realizations* or *samples*. How do we find *probabilities*?





Discretize the order parameter into a number of bins.

For every individual bin, we can do Boltzmann reweighting between ensembles.

$$\pi_i^{(k)} = \frac{\pi_i \exp[-b^{(k)}(i)]}{Z^{(k)}} \qquad\qquad Z^{(k)} = \sum_i \pi_i \exp[-b^{(k)}(i)]$$

where we have assumed that bias energy is constant over each bin.

But how to we find π_i?

Optimize likelihood: $L_{\mathrm{WHAM}}(\pi_i^{(k)}) = \prod_k \prod_i \left(\pi_i^{(k)}\right)^{N_i^{(k)}}$ (see next slide)

Maximum likelihood estimation

Start from basic definition of conditional probability:

$$Pr(\text{data}, \text{model}) = Pr(\text{ data} \mid \text{model }) \cdot Pr(\text{model})$$

$$= Pr(\text{model} \mid \text{data}) \cdot Pr(\text{data})$$

$$\max_{\text{models}} \underset{\substack{\uparrow \\ \text{posterior}}}{Pr(\text{ model} \mid \text{data })} = \underset{\substack{\uparrow \\ \text{likelihood } L}}{Pr(\text{data} \mid \text{model})} \frac{Pr(\text{model})}{\cancel{Pr(\text{data})}} \nwarrow \text{prior}$$

Because we don‘t know better: $Pr(\text{model}) = const$

Compute:

$$\max_{\text{models}} Pr(\text{data} \mid \text{model})$$

Likelihood for WHAM

Likelihood: $L_{\mathrm{WHAM}} = \prod_k \prod_i \left(\pi_i^{(k)}\right)^{N_i^{(k)}}$

Example: set of samples $\{1,2,3,3,2\}$ form simulation with umbrella 1

$$Pr(\{1,2,3,3,2\}) = \pi_1^{(1)}\pi_2^{(1)}\pi_3^{(1)}\pi_3^{(1)}\pi_2^{(1)} = \left(\pi_1^{(1)}\right)^1 \left(\pi_2^{(1)}\right)^2 \left(\pi_3^{(1)}\right)^2$$

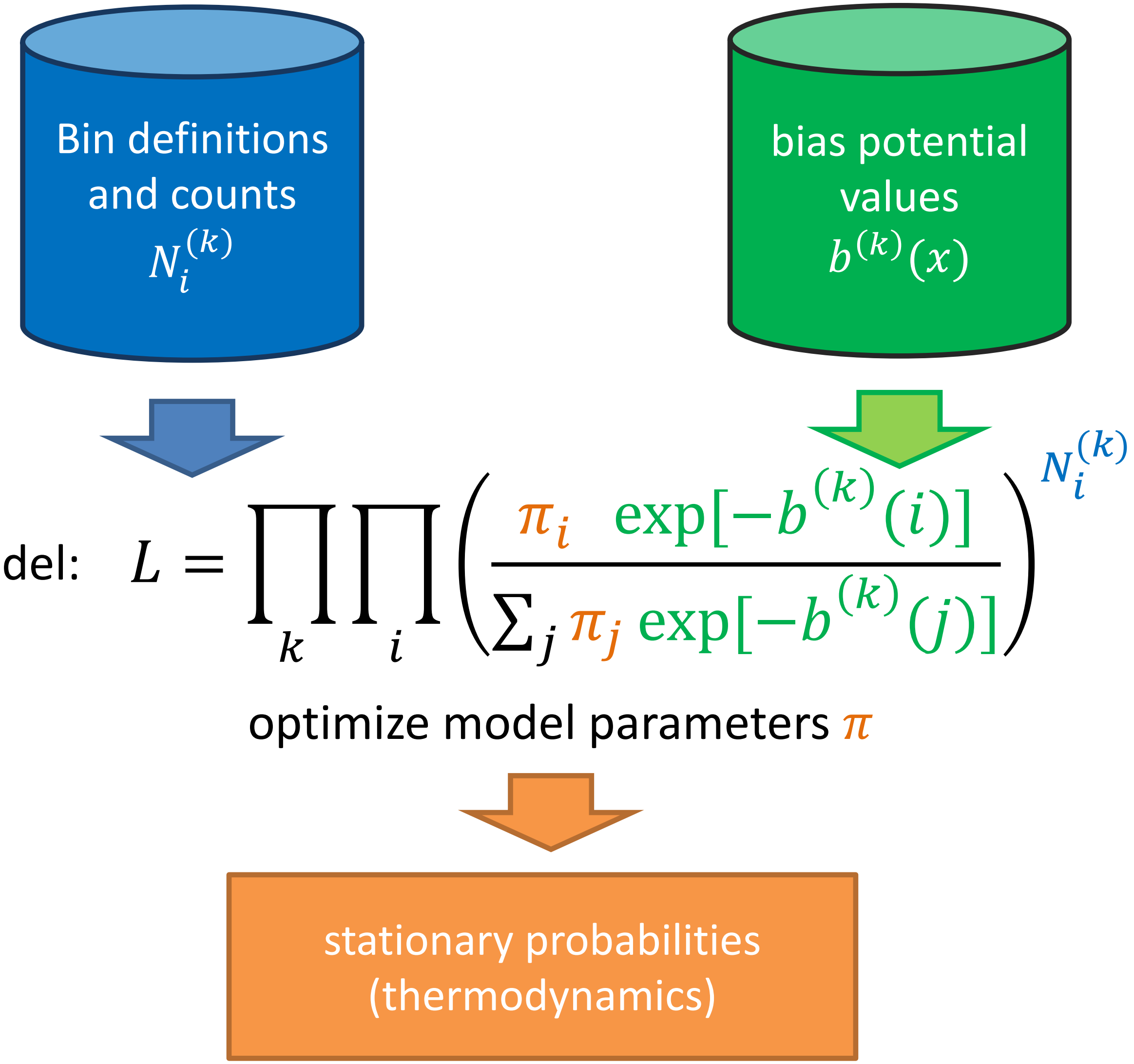
All simulations and all samples are statistically independent.
Inserting the Boltzmann reweighting relation into L_{WHAM} gives:

$$L(\pi_1, \dots, \pi_n) = \prod_k \prod_i \left(\frac{\pi_i \ \exp[-b^{(k)}(i)]}{\sum_j \pi_j \exp[-b^{(k)}(j)]} \right)^{N_i^{(k)}}$$

with the data $N_i^{(k)}$, $\exp[-b^{(k)}(i)]$ and the model parameters π_i.

Note: can make bins so small s. t. they contain only one x. $i \longrightarrow x$.

WHAM workflow



Bin definitions and counts $N_i^{(k)}$

bias potential values $b^{(k)}(x)$

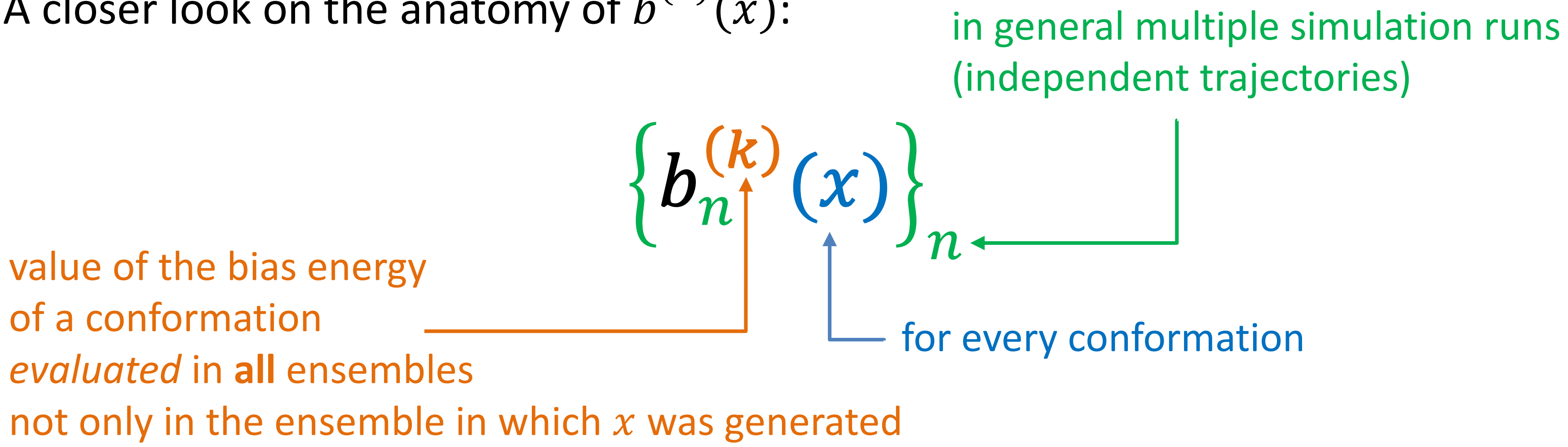
probabilistic model: $$L = \prod_k \prod_i \left(\frac{\pi_i \ \exp[-b^{(k)}(i)]}{\sum_j \pi_j \exp[-b^{(k)}(j)]} \right)^{N_i^{(k)}}$$

optimize model parameters π

stationary probabilities (thermodynamics)

Computing the bias energies

A closer look on the anatomy of $b^{(k)}(x)$:



$$\left\{b_n^{(k)}(x)\right\}_n$$

in general multiple simulation runs (independent trajectories)

value of the bias energy of a conformation *evaluated* in **all** ensembles not only in the ensemble in which x was generated

for every conformation

- This is 3-D data structure.
- Since the trajectories might have different lengths this is a jagged/ragged array and not a tensor. In PyEmma it’s a list of 2-D numpy arrays:

```
btrajs = [
    np.array([[0.0, ...], [1.2, ...]]),
    np.array([[0.0, ...], [4.2, ...]]),
    ...
]
```

Computing the bias energies

Example: Umbrella sampling

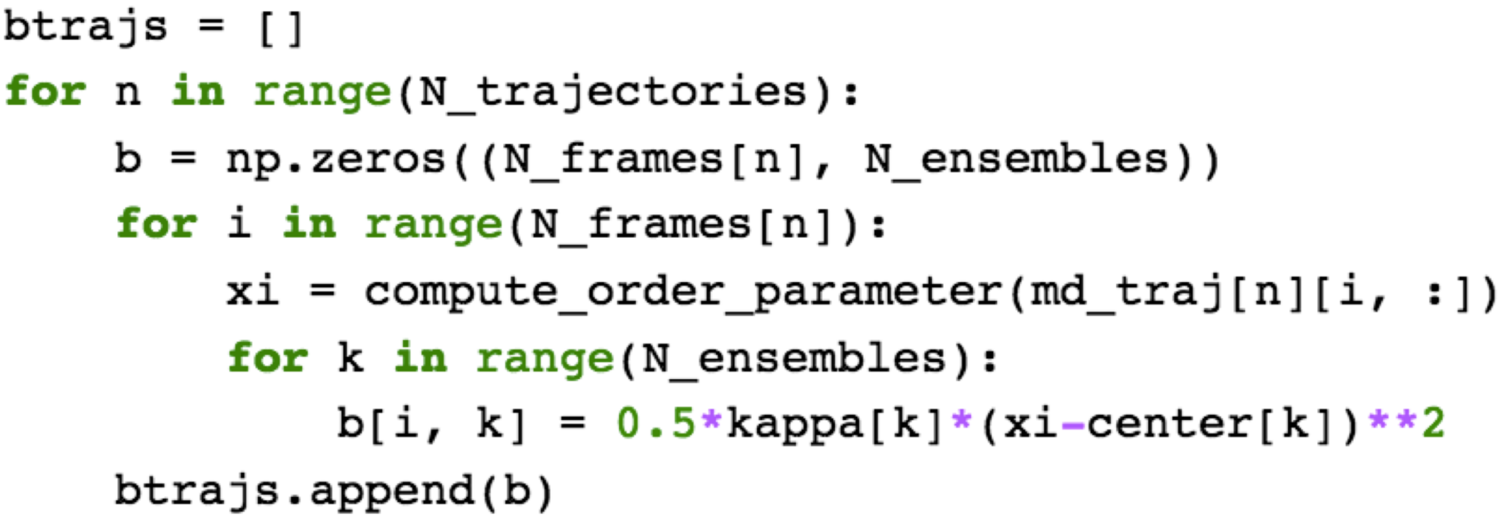
- All temperatures are the same

$$\beta^{(k)} = \beta = 1/k_B T = 1/(0.00198\,\mathrm{kcal/mol\,K} \cdot 300\,K)$$

- The bias is a quadratic function of an order parameter $\xi(x)$

$$U^{(k)}(x) = \frac{1}{2}\kappa^{(k)}\left(\xi(x) - \xi_{\mathrm{center}}^{(k)}\right)^2$$

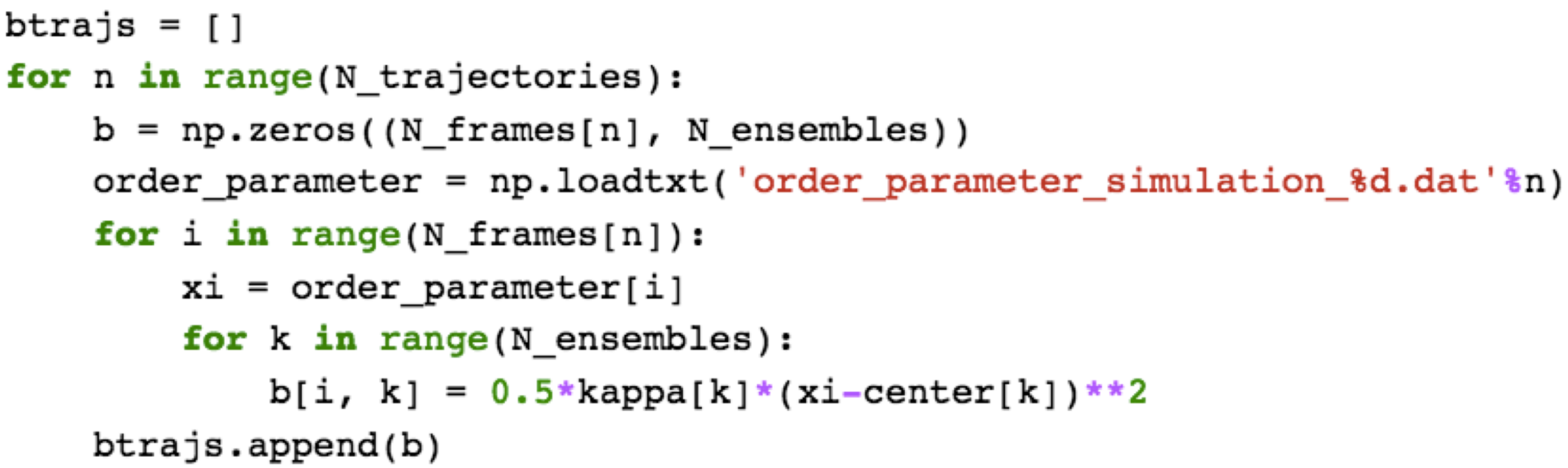
with the spring constants $\kappa^{(k)}$ and rest positions $\xi_{\mathrm{center}}^{(k)}$.



```
btrajs = []
for n in range(N_trajectories):
    b = np.zeros((N_frames[n], N_ensembles))
    for i in range(N_frames[n]):
        xi = compute_order_parameter(md_traj[n][i, :])
        for k in range(N_ensembles):
            b[i, k] = 0.5*kappa[k]*(xi-center[k])**2
    btrajs.append(b)
```

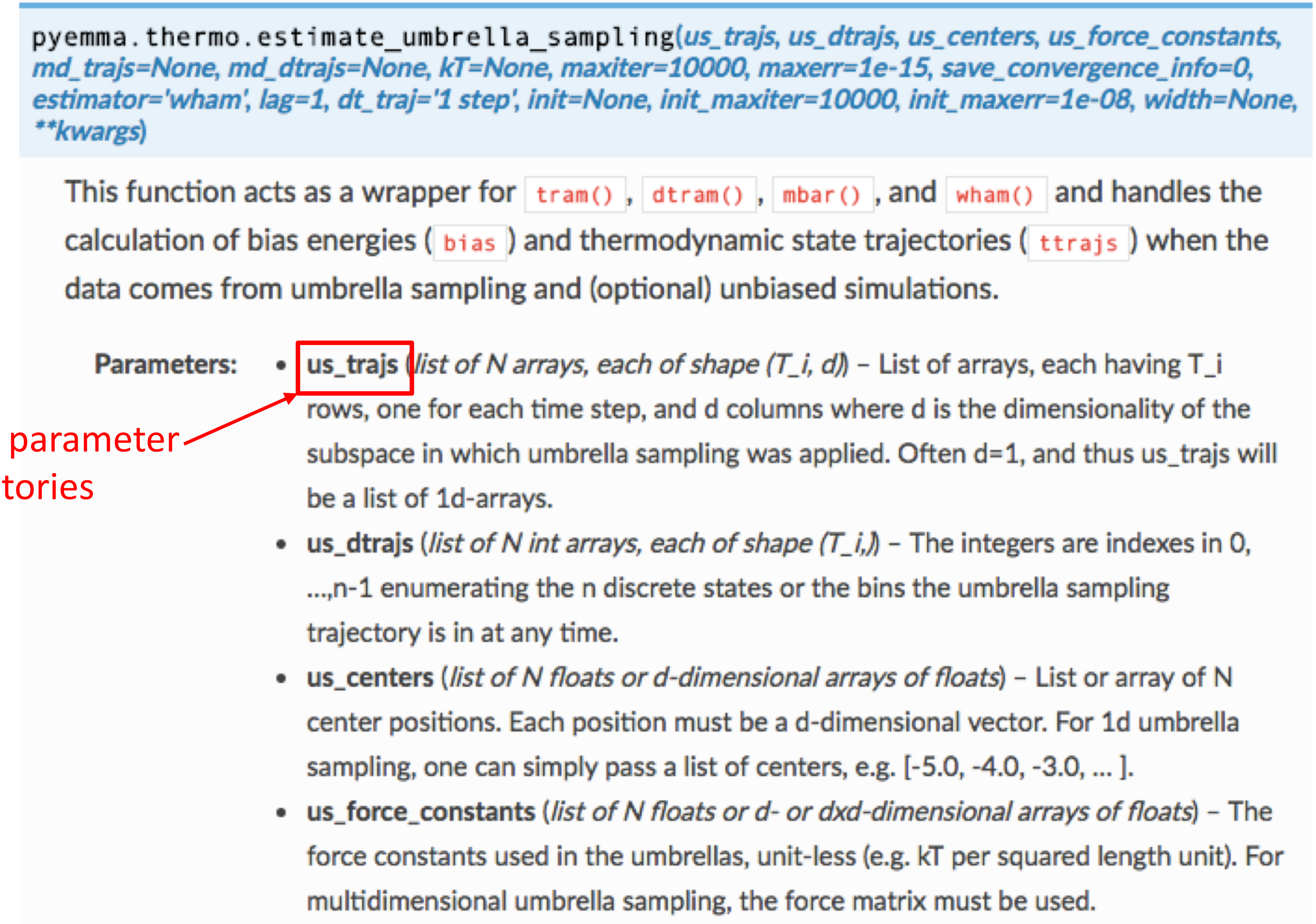
Computing the bias energies

Working with saved (pre-computed) order parameters:



```
btrajs = []
for n in range(N_trajectories):
    b = np.zeros((N_frames[n], N_ensembles))
    order_parameter = np.loadtxt('order_parameter_simulation_%d.dat'%n)
    for i in range(N_frames[n]):
        xi = order_parameter[i]
        for k in range(N_ensembles):
            b[i, k] = 0.5*kappa[k]*(xi-center[k])**2
    btrajs.append(b)
```

NOT computing the bias energies



`pyemma.thermo.estimate_umbrella_sampling(`*us_trajs, us_dtrajs, us_centers, us_force_constants, md_trajs=None, md_dtrajs=None, kT=None, maxiter=10000, maxerr=1e-15, save_convergence_info=0, estimator='wham', lag=1, dt_traj='1 step', init=None, init_maxiter=10000, init_maxerr=1e-08, width=None, **kwargs*`)`

This function acts as a wrapper for `tram()`, `dtram()`, `mbar()`, and `wham()` and handles the calculation of bias energies (`bias`) and thermodynamic state trajectories (`ttrajs`) when the data comes from umbrella sampling and (optional) unbiased simulations.

Parameters:

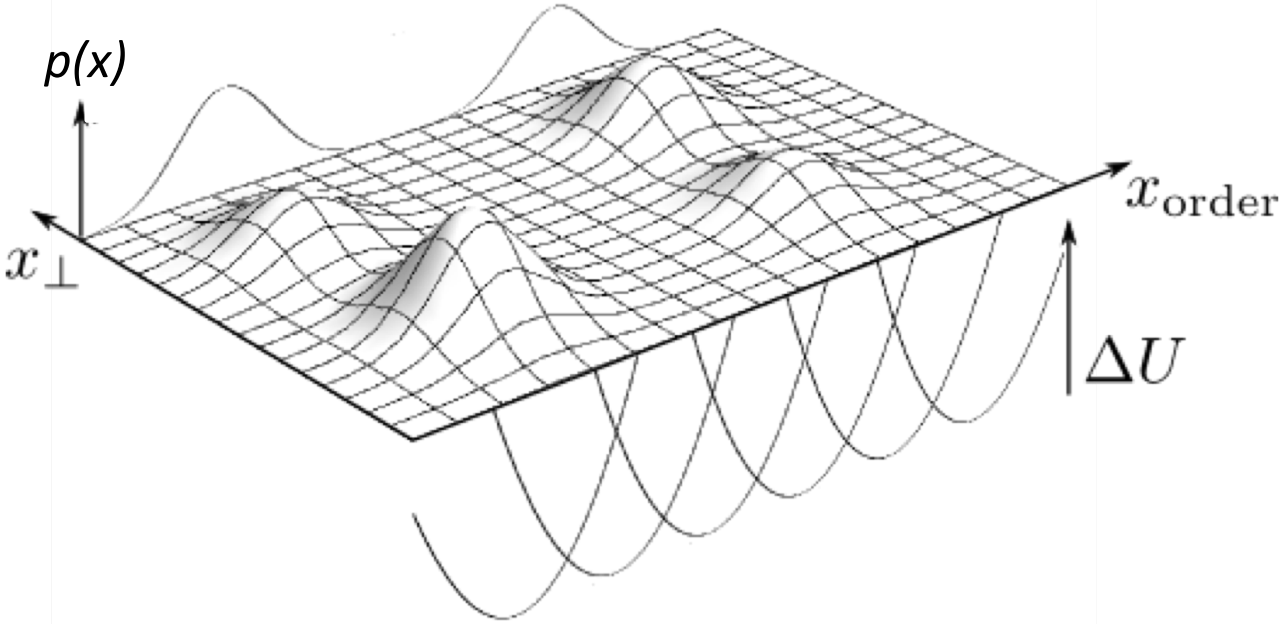
- **us_trajs** (*list of N arrays, each of shape (T_i, d)*) – List of arrays, each having T_i rows, one for each time step, and d columns where d is the dimensionality of the subspace in which umbrella sampling was applied. Often d=1, and thus us_trajs will be a list of 1d-arrays.
- **us_dtrajs** (*list of N int arrays, each of shape (T_i,)*) – The integers are indexes in 0,…,n-1 enumerating the n discrete states or the bins the umbrella sampling trajectory is in at any time.
- **us_centers** (*list of N floats or d-dimensional arrays of floats*) – List or array of N center positions. Each position must be a d-dimensional vector. For 1d umbrella sampling, one can simply pass a list of centers, e.g. [-5.0, -4.0, -3.0, …].
- **us_force_constants** (*list of N floats or d- or dxd-dimensional arrays of floats*) – The force constants used in the umbrellas, unit-less (e.g. kT per squared length unit). For multidimensional umbrella sampling, the force matrix must be used.

order parameter trajectories

- Pyemma example

Combining free energy calculations with MSMs: Multi Ensemble Markov Models

Problems of Umbrella sampling: slow orthogonal degrees of freedom

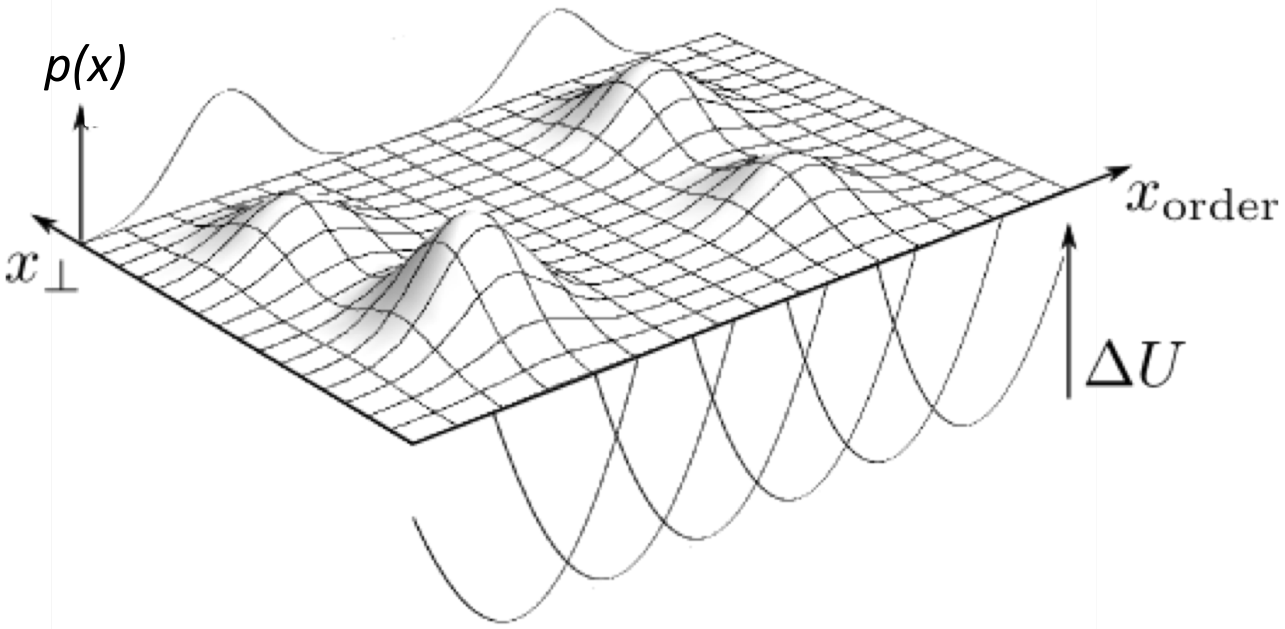


Remember the WHAM likelihood:

$$L_{\text{WHAM}} = \prod_k \prod_i \left(\pi_i^{(k)}\right)^{N_i^{(k)}}$$

Second product means that samples are drawn from the equilibrium distribution $\pi_i^{(k)}$.

Problems of Umbrella sampling: slow orthogonal degrees of freedom



In the energy landscape above, motion along $x_\perp$ can be highly autocorrelated. So the assumption of independent samples may be wrong. → systematic error

Since we know that MSMs can be used to compute free energies reliably form correlated data, can't we just somehow build an MSM along $x_\perp$?

MEMM

Multi **E**nsemble **M**arkov **M**odel $T_{ij}^{(k)}$

$$\begin{pmatrix} T_{11}^{(1)} & \cdots & T_{1n}^{(1)} \\ \vdots & \ddots & \vdots \\ T_{n1}^{(1)} & \cdots & T_{11}^{(1)} \end{pmatrix}$$

$$\begin{pmatrix} T_{11}^{(2)} & \cdots & T_{1n}^{(2)} \\ \vdots & \ddots & \vdots \\ T_{n1}^{(2)} & \cdots & T_{11}^{(2)} \end{pmatrix}$$

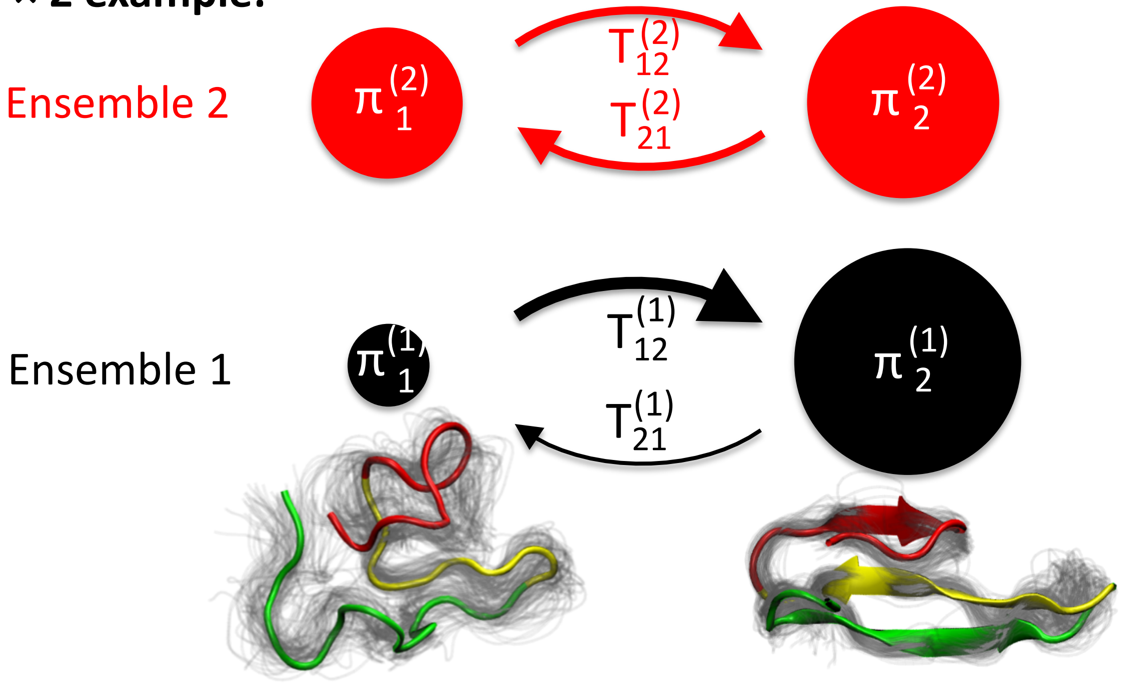
$$\vdots$$

$$\begin{pmatrix} T_{11}^{(K)} & \cdots & T_{1n}^{(K)} \\ \vdots & \ddots & \vdots \\ T_{n1}^{(K)} & \cdots & T_{11}^{(K)} \end{pmatrix}$$

index *k* = number of the Umbrella potential
= number of temperature in multi-temperature simulations

indices *i,j* = number of the discrete Markov state,
i.e. bin number along $x_\perp$
or any other sensible state discretization

2 × 2 example:



MEMM

Multi **E**nsemble **M**arkov **M**odel $T_{ij}^{(k)}$

- **How the individual MSMs in the MEMM are coupled together?**

- Part 1 of the answer:

Boltzmann reweighting of stationary distributions (like in WHAM)

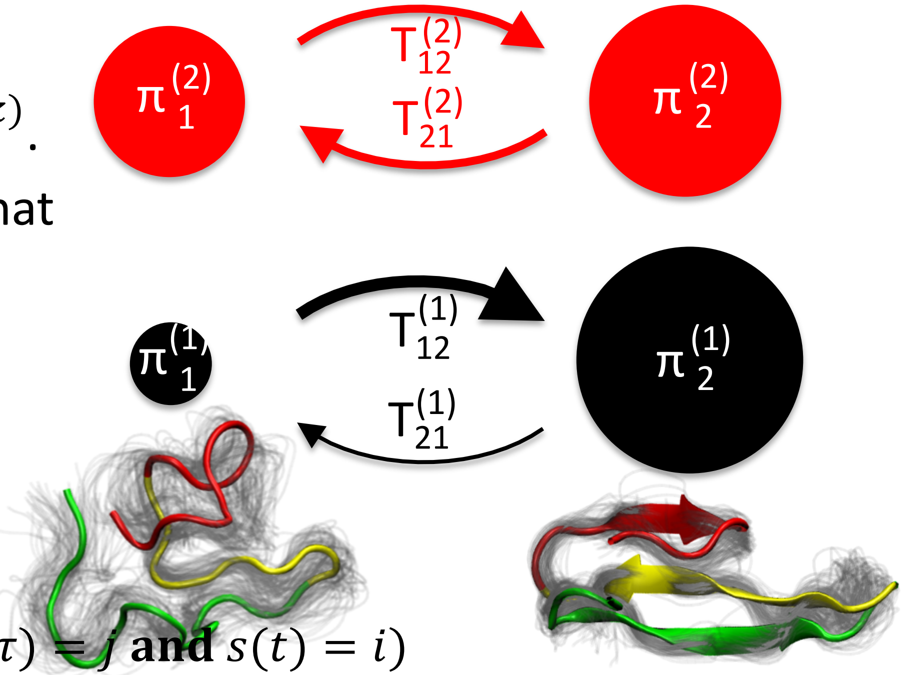
$$\pi_i^{(k)} = \frac{\pi_i \ \exp[-b^{(k)}(i)]}{Z^{(k)}} \qquad Z^{(k)} = \sum_i \pi_i \exp[-b^{(k)}(i)]$$

- Part 2 of the answer:

$\pi_i^{(k)}$ is the stationary distribution of $T_{ij}^{(k)}$.

We even require a stronger condition that $\mathbf{T}^{(k)}$ is reversible with respect to $\boldsymbol{\pi}^{(k)}$.

$$\pi_i^{(k)} T_{ij}^{(k)} = \pi_j^{(k)} T_{ji}^{(k)}$$



reversibility = detailed balance

$$\Pr(s(t+\tau) = i \ \textbf{and} \ s(t) = j) = \Pr(s(t+\tau) = j \ \textbf{and} \ s(t) = i)$$

(d)TRAM

(**d**iscrete) **T**ransition-based **R**eweighting **A**nalysis **M**ethod

- **How is the MEMM estimated?**

- **Reminder - estimation of MEMs:**

Likelihood for an MSM: $L_{\mathrm{MSM}} = \prod_i \prod_j \left(T_{ij}\right)^{C_{ij}}$

Consider example trajectory (1 → 2 → 2 → 1 → 2)

$$\Pr(1 \to 2 \to 2 \to 1 \to 2) = \Pr(1) \cdot T_{12} \cdot T_{22} \cdot T_{21} \cdot T_{12}$$

$$\propto (T_{11})^0 (T_{12})^2 (T_{22})^1 (T_{21})^1$$

$$= (T_{11})^{C_{11}} (T_{12})^{C_{12}} (T_{22})^{C_{22}} (T_{21})^{C_{21}}$$

$$= \prod_{i=1}^{2} \prod_{j=1}^{2} \left(T_{ij}\right)^{C_{ij}}$$

(d)TRAM

(**d**iscrete) **T**ransition-based **R**eweighting **A**nalysis **M**ethod

- **How is the MEMM estimated?**

Basically **an MEMM is just a collection of MSMs**.

$$L_{\mathrm{MEMM}}(\mathbf{T}^{(1)}, \dots, \mathbf{T}^{(K)}) = \prod_{k} L_{\mathrm{MSM}}(\mathbf{T}^{(k)})$$

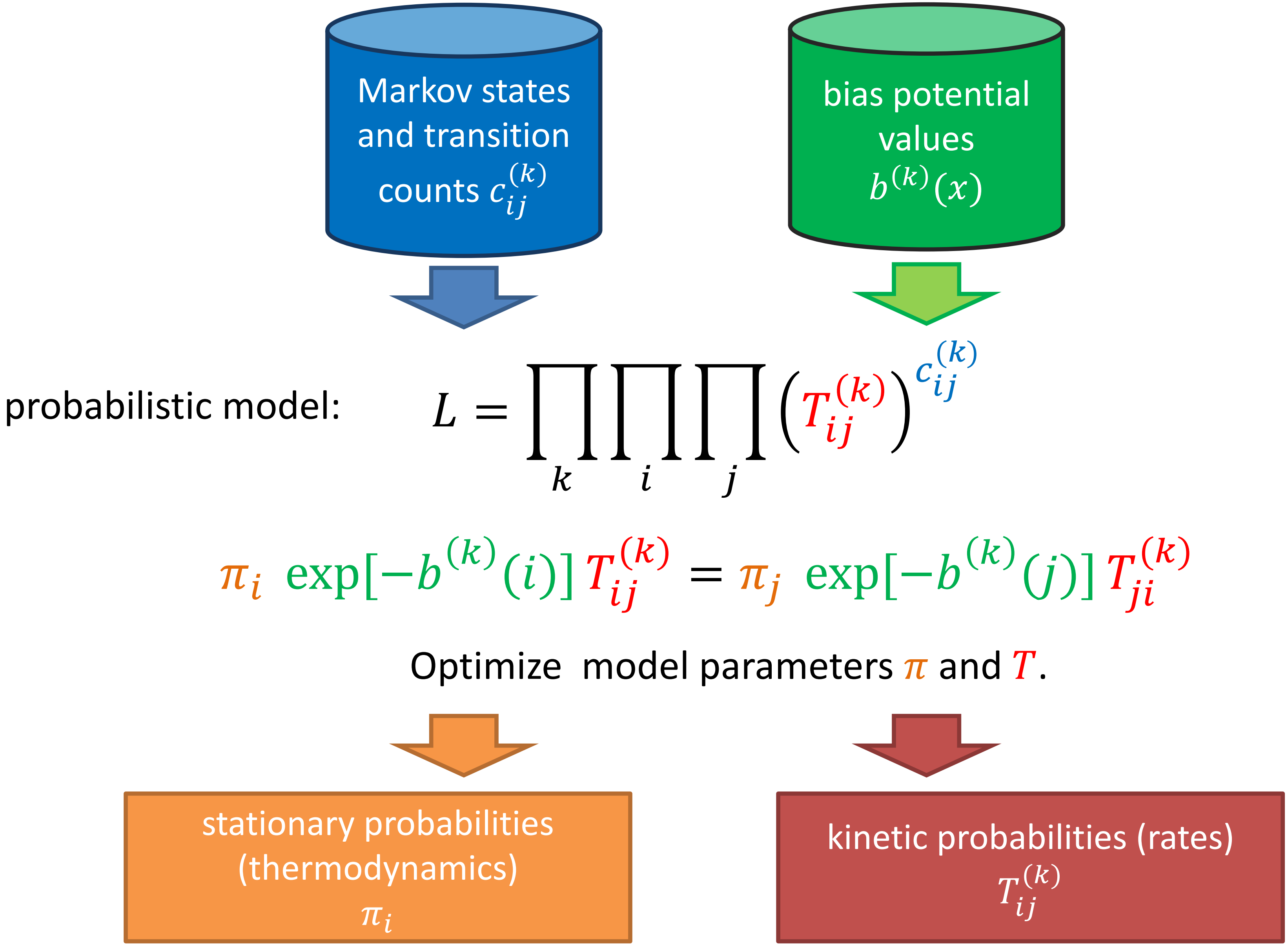
Inserting gives:

$$L_{\mathrm{MEMM}} = \prod_{k} \prod_{i} \prod_{j} \left(T_{ij}^{(k)}\right)^{C_{ij}^{(k)}}$$

Maximize L_{MEMM} under the constraints:

- $\pi_i^{(k)} T_{ij}^{(k)} = \pi_j^{(k)} T_{ji}^{(k)}$
- $\sum_j T_{ij}^{(k)} = 1$
- $\pi_i^{(k)} = \frac{\pi_i \ \exp[-b^{(k)}(i)]}{\sum_j \pi_j \exp[-b^{(k)}(j)]}$
- $T_{ij}^{(k)} \geq 0$

(d)TRAM: workflow



Markov states and transition counts $c_{ij}^{(k)}$

bias potential values $b^{(k)}(x)$

probabilistic model:

$$L = \prod_k \prod_i \prod_j \left(T_{ij}^{(k)}\right)^{c_{ij}^{(k)}}$$

$$\pi_i \ \exp[-b^{(k)}(i)]\, T_{ij}^{(k)} = \pi_j \ \exp[-b^{(k)}(j)]\, T_{ji}^{(k)}$$

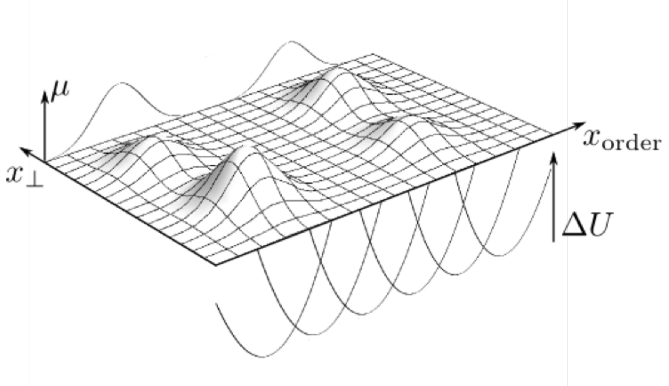
Optimize model parameters π and T.

stationary probabilities (thermodynamics) π_i

kinetic probabilities (rates) $T_{ij}^{(k)}$

Advantages of using (d)TRAM

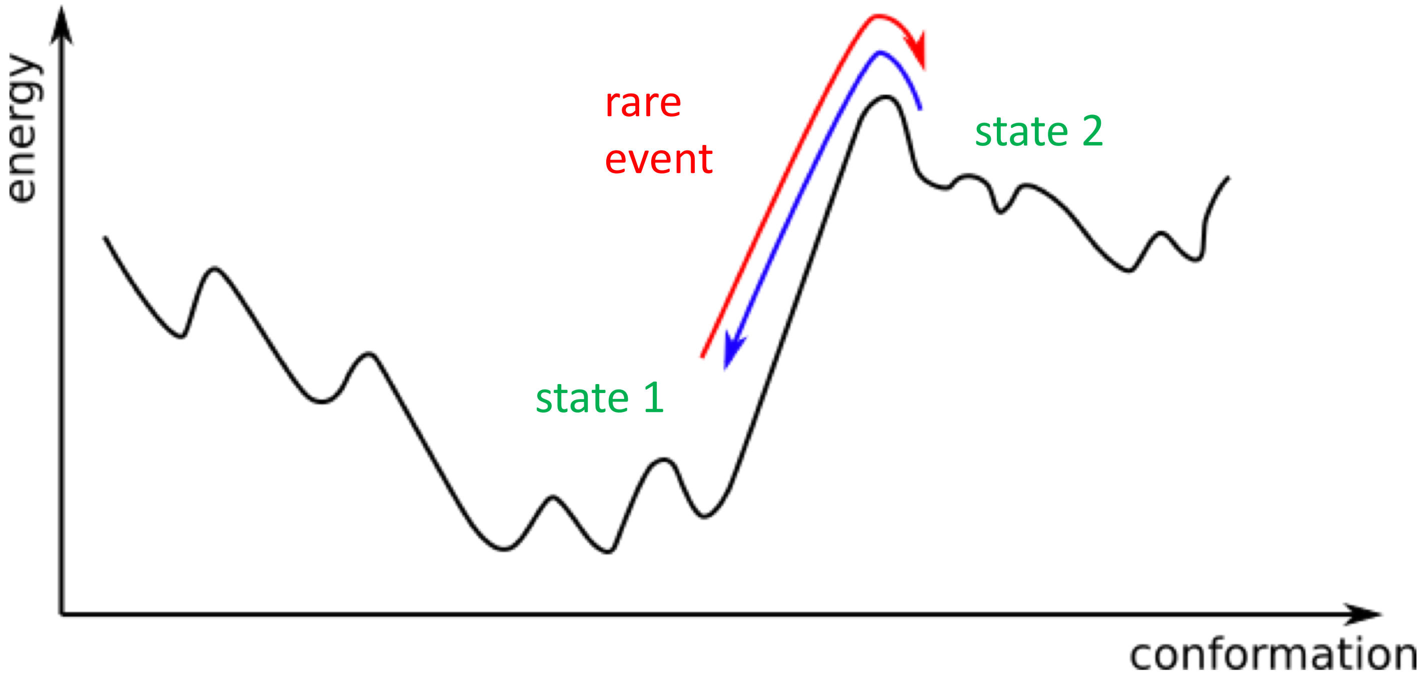
- Better estimation of free energies along the unbiased orthogonal degrees of freedom.



- There is no initial equilibration transient where the simulation have to relax to global equilibrium.

- Smaller de-correlation time (simulation time until one gets a new uncorrelated frame). More efficient usage of the data.

Advantages of using (d)TRAM



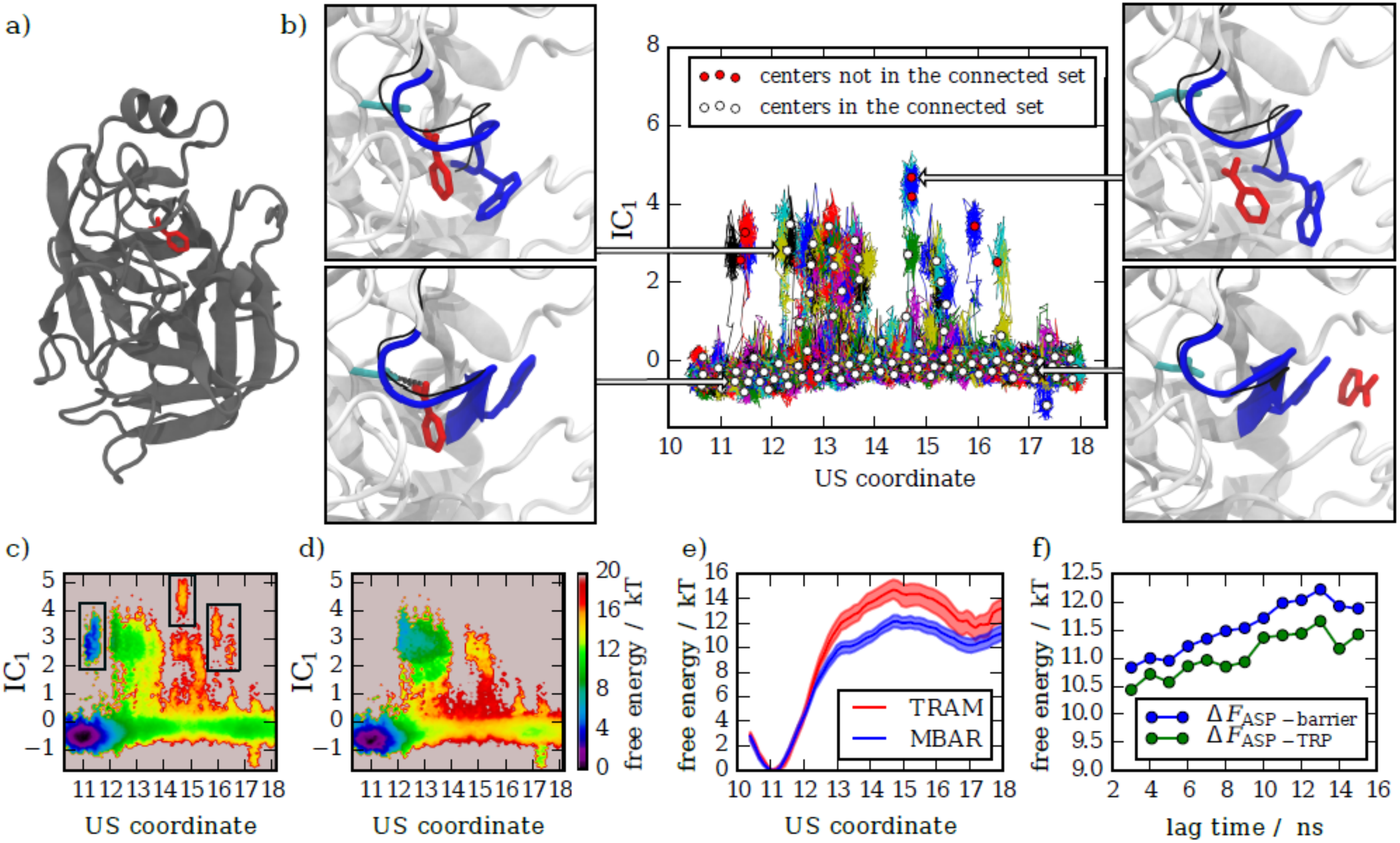
T_{12} is a small number, hard to simulate.
T_{21} can be estimated easily from direct simulation.

$$\pi_i \ T_{ij} \ = \pi_j \ T_{ji}$$

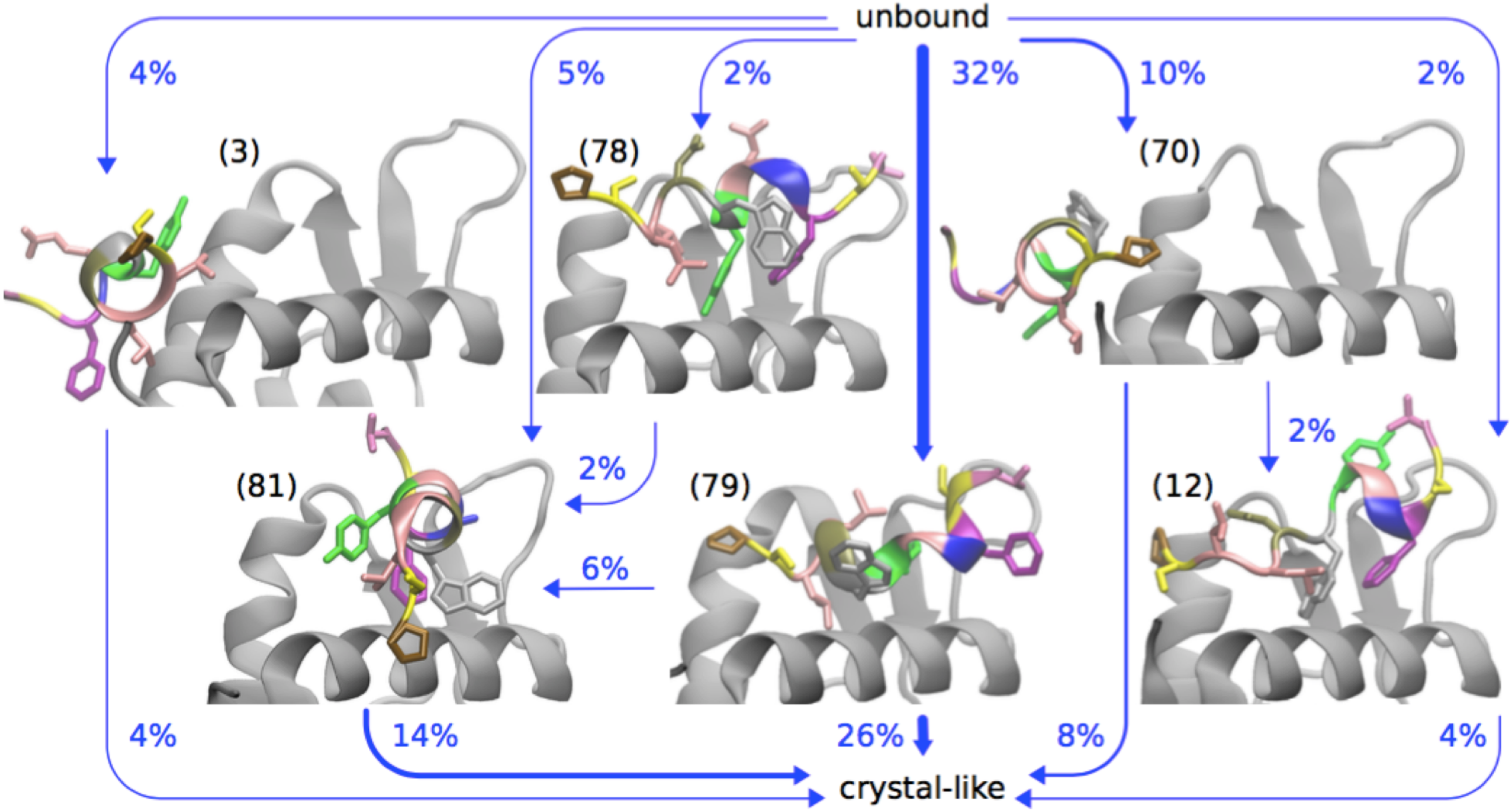
If we know T_{21} and π_2/π_1 , we don‘t have to simulate the uphill 1 → 2 transition.

Real-world applications

Application 1: Trypsin-Benzamidine



Application 2: PMI-Mdm2

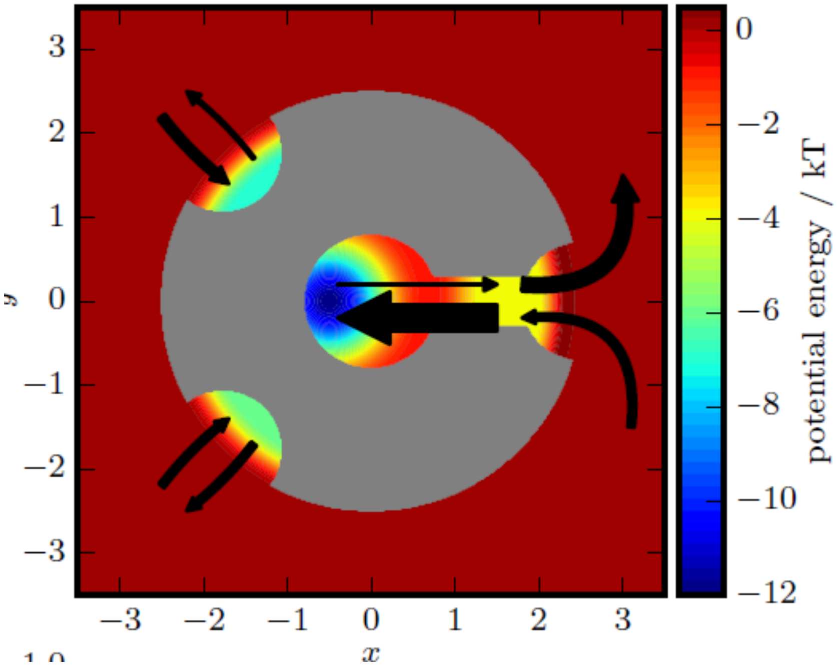


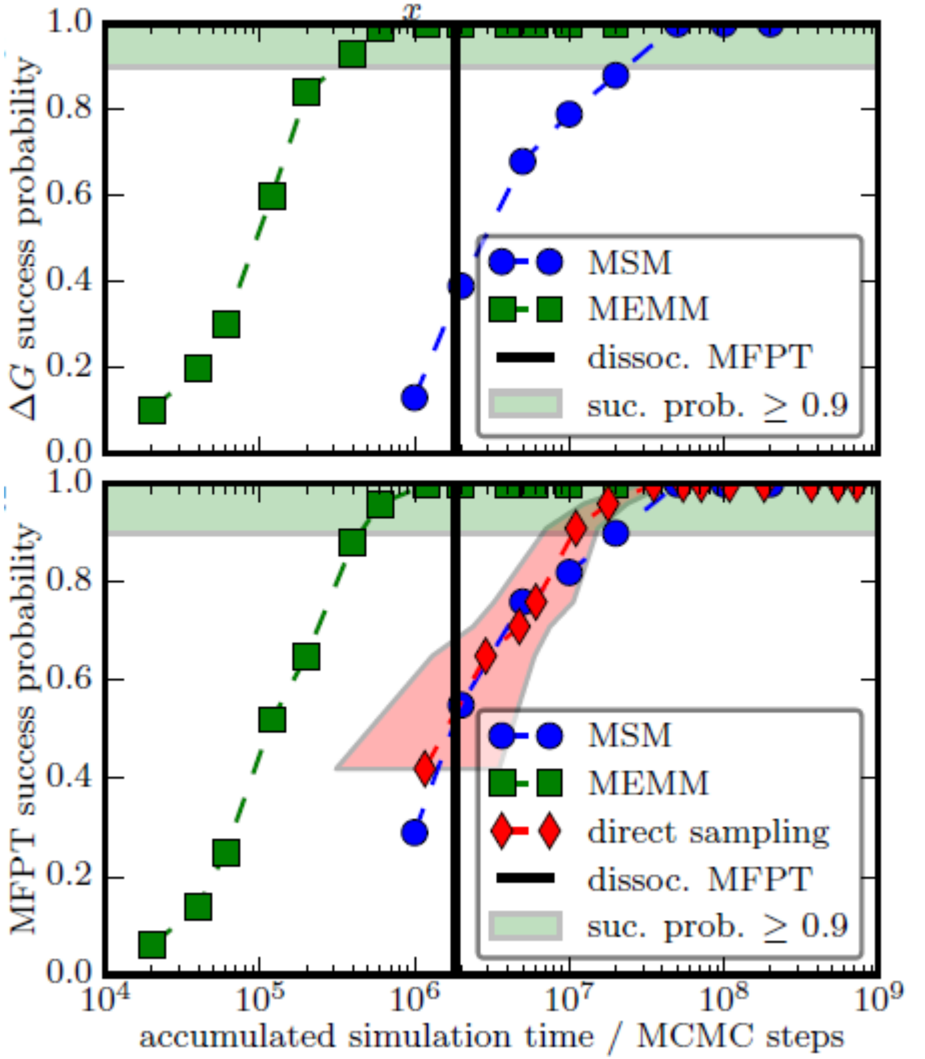
Further reading

- Wu, Mey, Rosta, Noé: “Statistically optimal analysis of state-discretized trajectory data from multiple thermodynamic states”, *J. Chem. Phys.* **141**, 214106 (2014)
- Wu, Paul, Wehmeyer, Noé: “Multiensemble Markov models of molecular thermodynamics and kinetics”, *PNAS* **113**, E3221–E3230 (2016)
- Paul *et al.* “Protein-peptide association kinetics beyond the seconds timescale from atomistic simulations” *Nat. Commun.,* **8**, 1095 (2017)

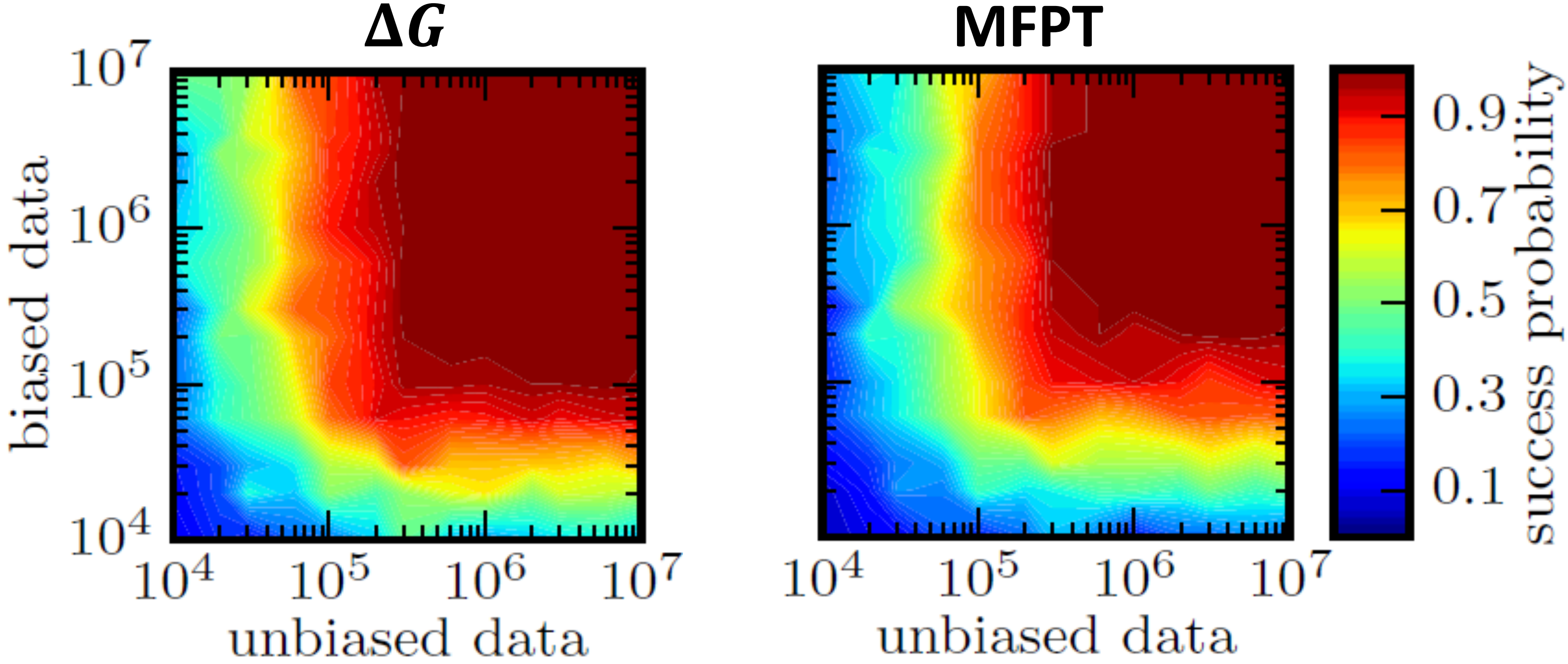
TRAM: strategies for enhanced sampling of kinetics

Model system:





TRAM: strategies for enhanced sampling of kinetics

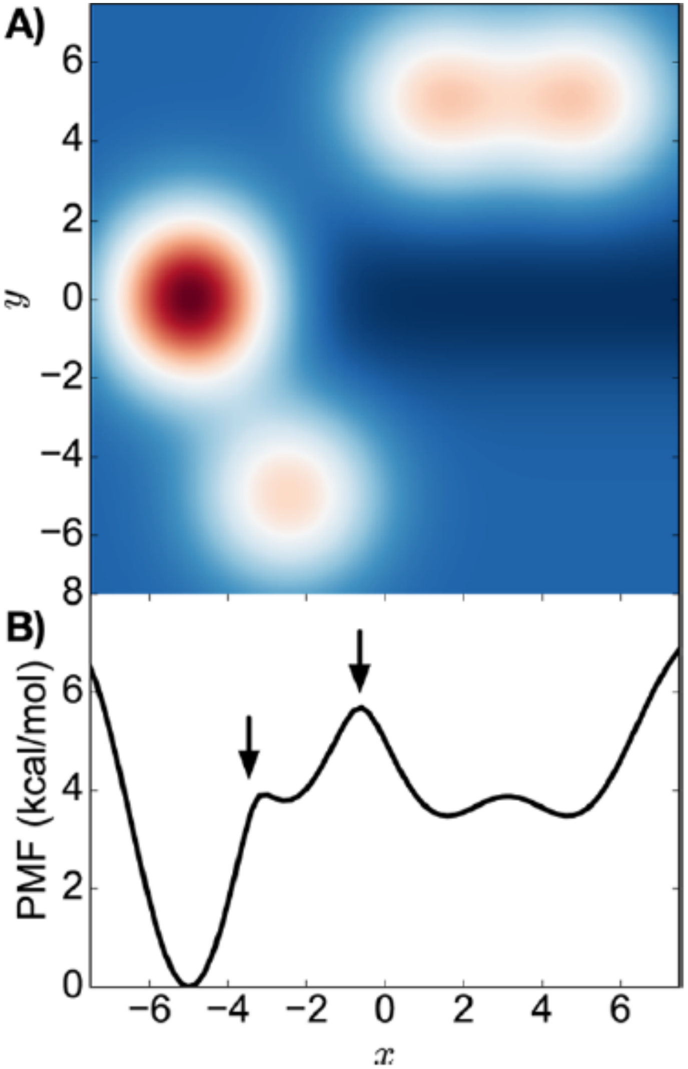


ΔG

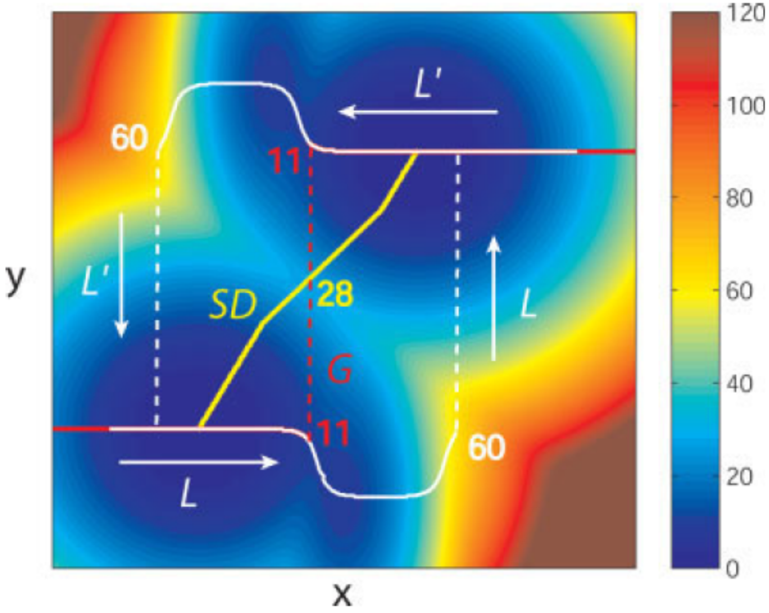
MFPT

What is valid input data for TRAM?

Overlap in (d)TRAM

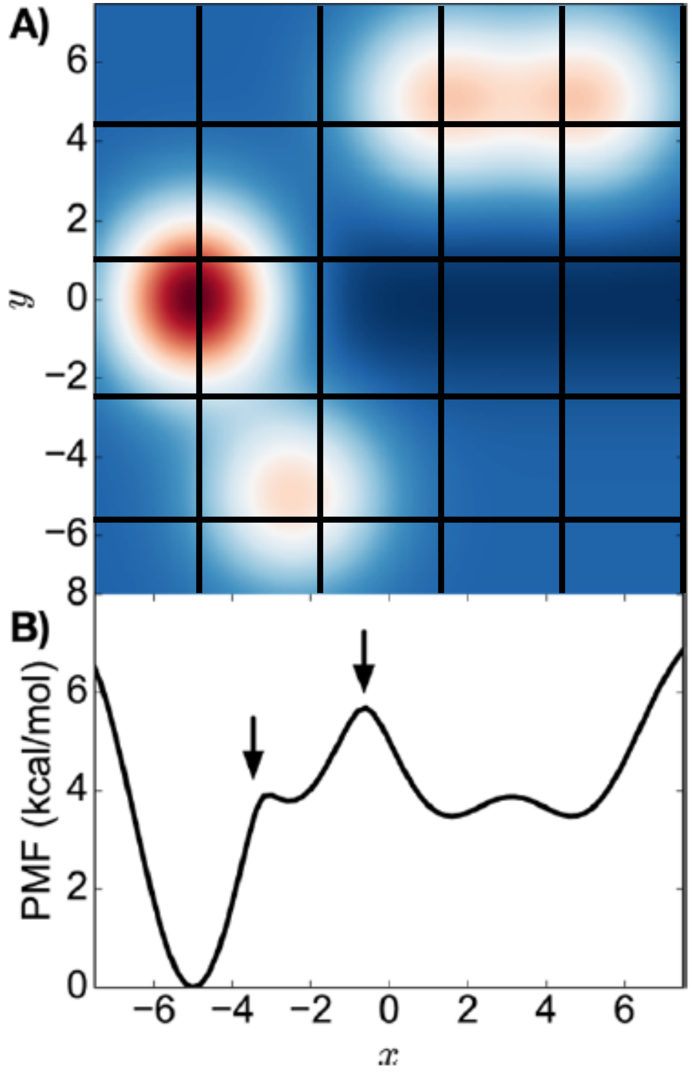


Jo *et al, J. Phys. Chem. B* **120** 8733 (2016)

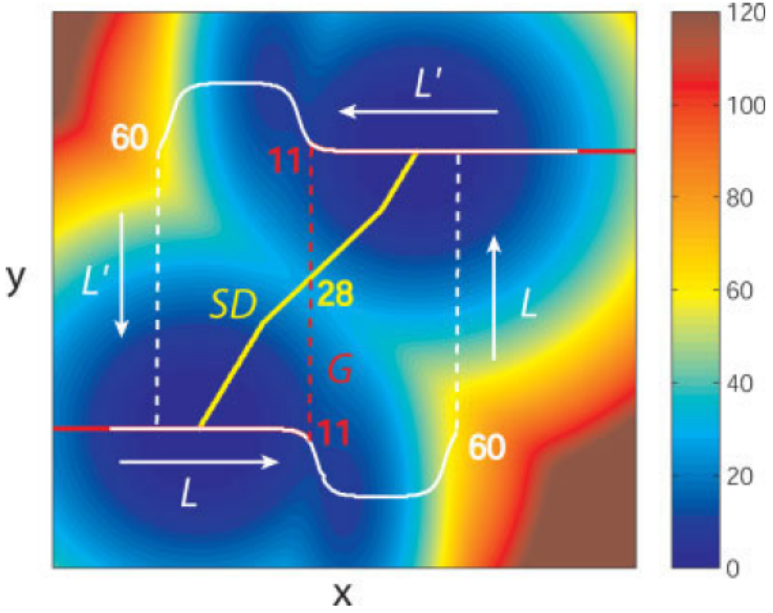


Rosta *et al, J. Comput. Chem.* **30**, 1634 (2009)

Overlap in (d)TRAM



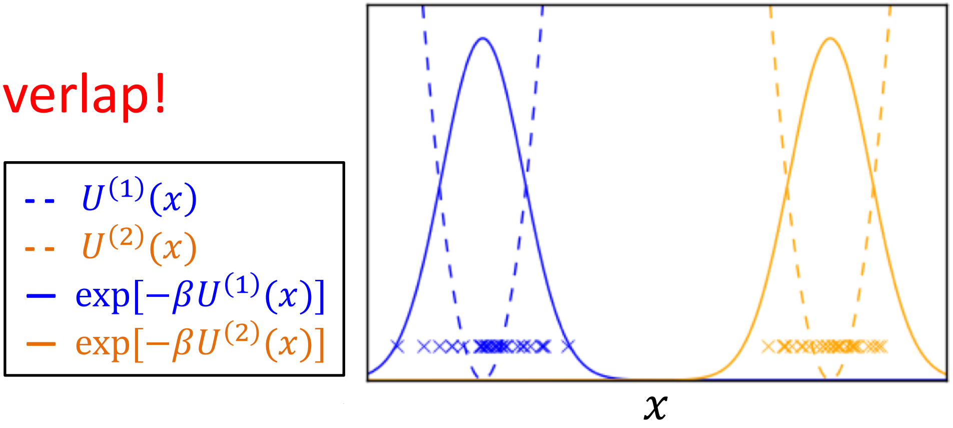
Jo *et al, J. Phys. Chem. B* **120** 8733 (2016)



Rosta *et al, J. Comput. Chem.* **30**, 1634 (2009)

Overlap of biased distributions

Biased distributions have to overlap!



Diagnostics:

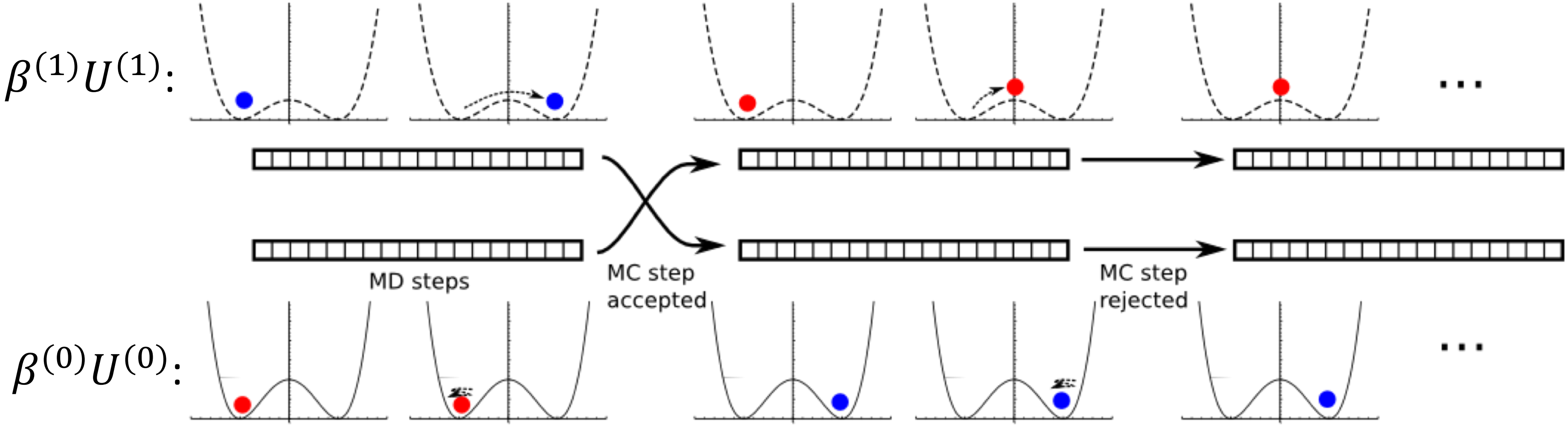
- Post-hoc replica exchange: How many exchanges would have been accepted if the simulation had been carried out with replica exchange between ensembles? How does this number compare to the number of simulated samples?

$$\text{score} = (N+M)\frac{1}{N\,M}\sum_{x\in X^{(k)}}\sum_{y\in X^{(l)}}\min\left[1,\frac{e^{-\beta U^{(k)}(x)}e^{-\beta U^{(l)}(y)}}{e^{-\beta U^{(k)}(y)}e^{-\beta U^{(l)}(x)}}\right] \leqslant 1$$

- error of the free energies estimated by (M)BAR (equation from [1]). Alternative way to relate the overlap of distributions to the number of samples.

[1] Shirts and Chodera, Statistically optimal analysis of samples from multiple equilibrium states, J. Chem. Phys. 129, 124105 (2008)

What is replica exchange?



- sample from generalized ensemble :

$$p(x_i, x_j, \ldots, x_k) = \frac{\mathrm{e}^{-\beta^{(0)}U^{(0)}(x_i)}}{Z^{(0)}} \cdot \frac{\mathrm{e}^{-\beta^{(1)}U^{(1)}(x_j)}}{Z^{(1)}} \cdot \ldots \cdot \frac{\mathrm{e}^{-\beta^{(K)}U^{(K)}(x_K)}}{Z^{(K)}}$$

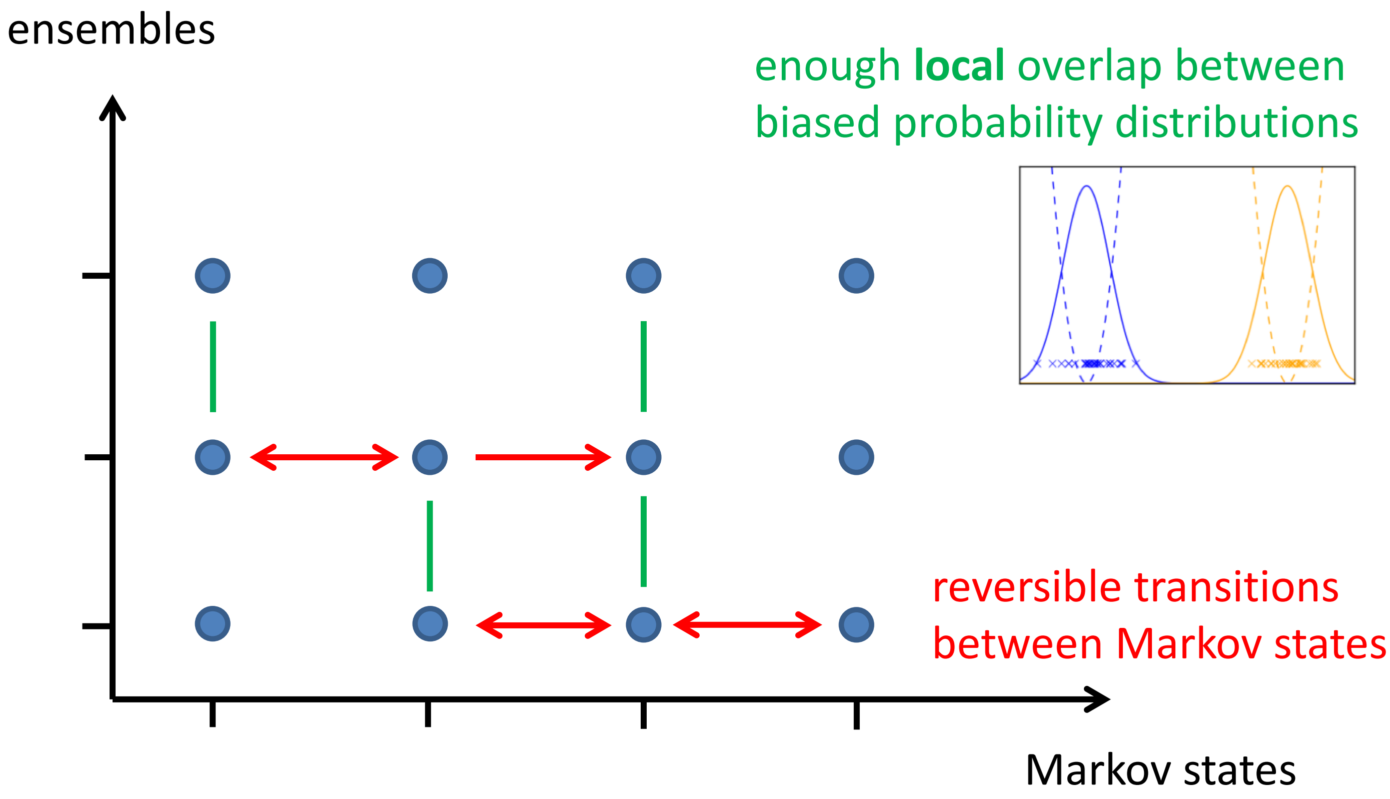
- accept exchanges with Metropolis criterion

$$p_{\mathrm{accept}} = \min\left[1, \frac{\mathrm{e}^{-\beta^{(1)}U^{(1)}(x_2)}\mathrm{e}^{-\beta^{(2)}U^{(2)}(x_1)}}{\mathrm{e}^{-\beta^{(1)}U^{(1)}(x_1)}\mathrm{e}^{-\beta^{(2)}U^{(2)}(x_2)}}\right]$$

with labels updated after an accepted exchange.

Fukunishi and Watanabe, *J. Chem. Phys*. **116,** 9058 (2002)

Overlap in (d)TRAM



ensembles

enough **local** overlap between biased probability distributions

reversible transitions between Markov states

Markov states

Much of this is based on empirical evidence from numerical examples.

summary

- We have introduced the TRAM method which combines Boltzmann reweighting and Markov state models. It replace the histogram-based analysis methods with transition-based methods.
- TRAM allows to combine free-energy calculation (for which we have many tools) with direct MD simulation of the downhill processes (which are easy) to obtain an optimal estimate of the full unbiased kinetics.

Further reading

- Wu, Mey, Rosta, Noé: "Statistically optimal analysis of state-discretized trajectory data from multiple thermodynamic states", *J. Chem. Phys.* **141** 214106 (2014)
- Wu, Paul, Wehmeyer, Noé: "Multiensemble Markov models of molecular thermodynamics and kinetics", *PNAS* E3221–E3230 (2016)

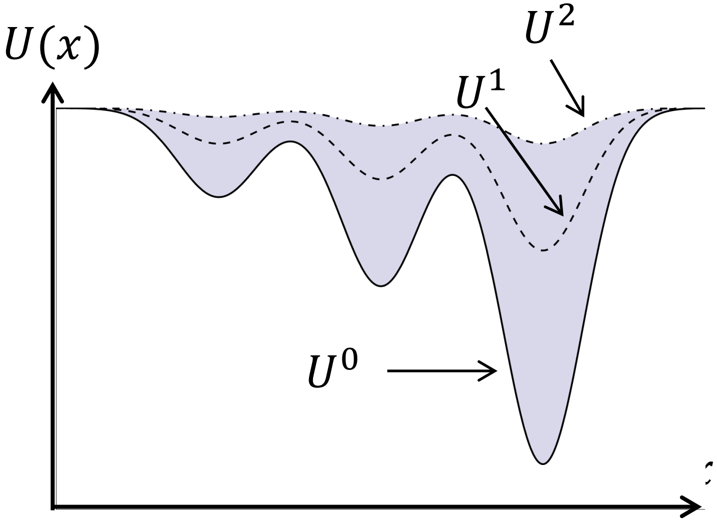
TRAM: Boltzmann reweighting

$$\langle O \rangle^i = \int O(x) p^i(x) \mathrm{d}x \approx \frac{1}{N} \sum_n^N O(x_n)$$

importance sampling

$$\langle O \rangle^i = \int O(x) p^j(x) \frac{p^i(x)}{p^j(x)} \mathrm{d}x$$

$$\approx \tfrac{1}{N} \sum_n^N O(x_n) \frac{p^i(x_n)}{p^j(x_n)}$$

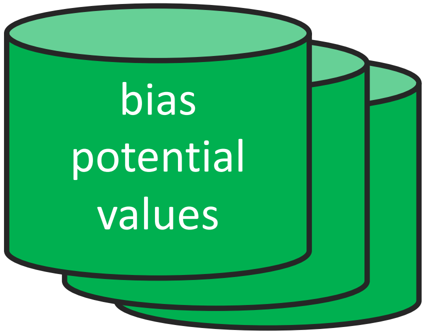


in chemistry

$$p^i(x) = e^{\beta F^i - \beta U^i(x)}$$

TRAM: combining normal MD with biased MD

Markov states and transition counts


bias potential values

probabilistic model: $$L = \prod_{i,j,k} \left(T_{ij}^{k}\right)^{c_{ij}^{k}} \cdot \prod_{k} \prod_{x \in X^{k}} \frac{e^{-b^{k}(x)}\mu(x)}{z_{s(x)}^{k}}$$

$$z_i^k T_{ij}^k = z_j^k T_{ji}^k$$

optimize model parameters T and μ (and z[μ])

stationary probabilities (thermodynamics)

kinetic probabilities (rates)

WHAM derivation

$$\log L = \sum\nolimits_{i,k} N_i^{(k)} \log \pi_i^{(k)}$$

$$= \sum\nolimits_{i,k} N_i^{(k)} \log \left(\frac{\pi_i \gamma_i^{(k)}}{\sum_j \pi_j \gamma_j^{(k)}} \right)$$

$$= \sum\nolimits_{i,k} N_i^{(k)} \log \pi_i \gamma_i^{(k)} - \sum\nolimits_{i,k} N_i^{(k)} \log \sum_j \pi_j \gamma_j^{(k)}$$

$$= \sum\nolimits_{i,k} N_i^{(k)} \log \pi_i \gamma_i^{(k)} - \sum\nolimits_k N^{(k)} \log \sum_j \pi_j \gamma_j^{(k)}$$

$$\frac{\partial L}{\partial \pi_n} = \sum\nolimits_k \frac{N_n^{(k)}}{\pi_n \gamma_n^{(k)}} \gamma_n^{(k)} - \sum\nolimits_k \frac{N^{(k)} \gamma_n^{(k)}}{\sum_j \pi_j \gamma_j^{(k)}} = 0$$

$$\frac{1}{\pi_n} \sum\nolimits_k N_n^{(k)} = \sum\nolimits_k \frac{N^{(k)} \gamma_n^{(k)}}{\sum_j \pi_j \gamma_j^{(k)}}$$

$$\pi_n = \frac{N_n}{\sum_k \frac{N^{(k)} \gamma_n^{(k)}}{\sum_j \pi_j \gamma_j^{(k)}}}$$

(d)TRAM: solution

update equations:

$$\pi_i^{\mathrm{new}} = \frac{\sum_{j,k} c_{ji}^{(k)}}{\sum_{l,j} \frac{\left(c_{ij}^{(l)}+c_{ji}^{(l)}\right)\gamma_i^{(l)}\nu_j^{(l)}}{\gamma_i^{(l)}\pi_i\nu_j^{(l)}+\gamma_j^{(l)}\pi_j\nu_i^{(l)}}}$$

$$\nu_i^{(k),\mathrm{new}} = \nu_i^{(k)} \sum_j \frac{\left(c_{ij}^{(k)} + c_{ji}^{(k)}\right)\gamma_j^{(k)}\pi_j}{\gamma_i^{(k)}\pi_i\nu_j^{(k)} + \gamma_j^{(k)}\pi_j\nu_i^{(k)}}$$

transition matrix:

$$T_{ij}^{(k)} = \frac{\left(c_{ij}^{(k)} + c_{ji}^{(k)}\right)\gamma_j^{(k)}\pi_j}{\gamma_i^{(k)}\pi_i\nu_j^{(k)} + \gamma_j^{(k)}\pi_j\nu_i^{(k)}}$$